CELL BIOLOGY

BASICS TO BREAKTHROUGHS

Editors:
K.N. Aruljothi
Prakash Gangadaran
Krishnan Anand
Satish Ramalingam
K. Kumaran
Kruthika Prakash

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Cell Biology: Basics to Breakthroughs

Edited by

K.N. Aruljothi
Department of Genetic Engineering, College of Engineering and Technology SRM Institute of Science and Technology, Kattankulathur, Chengalpattu Tamil Nadu, India

Prakash Gangadaran
Department of Medicine & Department of Nuclear Medicine. School of Medicine, Kyungpook National University. Daegu, Republic of Korea

Krishnan Anand
Department of Chemical Pathology, School of Pathology, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa

&

Satish Ramalingam, K. Kumaran & Kruthika Prakash
Department of Genetic Engineering, College of Engineering and Technology, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India

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Editors: K.N. Aruljothi, Prakash Gangadaran, Krishnan Anand, Satish Ramalingam, K. Kumaran & Kruthika Prakash

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FOREWORD

It is with great pleasure that I write this foreword for Dr. Kandasamy Nagarajan ArulJothi's remarkable book, Cell Biology: Basics to Breakthroughs. Dr. ArulJothi is a distinguished researcher and academician whose contributions to the fields of genetics, molecular biology, and precision medicine have significantly advanced our understanding of complex cellular processes. With over 70 scientific publications in renowned journals, his work spans diverse areas, including cancer biology, dyslipidemia, exosomal biomarkers, and stem cell therapy, making him a key figure in the field of biomedical research. His active participation in international collaborations, editorial board memberships, and ground-breaking research reflects his unwavering commitment to scientific excellence.

What makes this book particularly valuable is its dual focus on education and research. It serves as an essential resource not only for undergraduate and graduate students seeking to build a strong foundation in cell biology but also for researchers and educators looking to stay abreast of the latest scientific developments. The clear organization, coupled with detailed explanations, illustrative diagrams, and real-world applications, makes complex cellular processes accessible and engaging.

A unique highlight of Cell Biology: Basics to Breakthroughs is the scientific contributions from world-renowned experts in the field, who bring diverse insights and expertise. The book features Dr. Krishnan Anand from the University of the Free State, South Africa, whose work in cancer biology and molecular pathology adds depth to the chapters on cancer stem cells and therapeutic interventions. Dr. Satish Ramalingam from SRM University, a distinguished expert in molecular diagnostics and translational medicine, provides valuable perspectives on cell signaling and emerging therapeutic targets. Additionally, Dr. Prakash Gangadharan from the School of Medicine, Kyungpook National University, Republic of Korea, offers his expertise in cellular mechanisms of disease and regenerative medicine, enriching the book with clinically relevant insights. Their collaborative editorial contributions enhance the scientific rigor and global relevance of this volume, making it a truly comprehensive resource for cell biology enthusiasts and professionals alike.

Dr. ArulJothi's ability to integrate basic principles with translational insights makes Cell Biology: Basics to Breakthroughs a timely and impactful contribution to the field. By highlighting the clinical and therapeutic relevance of cell biology, this book has the potential to inspire future researchers and contribute to the advancement of biomedical science. I am confident that this book will serve as an invaluable reference for students, scientists, and educators alike, offering profound insights into the intricate world of cells and their role in health, disease, and biotechnology.

Prof. Surajit Pathak, Ph.D.
Medical Biotechnology Department
Faculty of Allied Health Sciences
Chettinad Hospital & Research Institute
Chettinad Academy of Research and Education
Chennai, India

PREFACE

A remarkable trip to the fundamental building blocks of life, cell biology reveals the complicated and crucial mechanisms that regulate the survival, development, and evolution of organisms. This area of study is an incredible adventure into the fundamental building blocks of life. The purpose of this book, titled Cell Biology: Basics to Breakthroughs, is to provide readers with a clear and thorough overview of both the fundamentals of cell biology and the most recent advancements in the field. Students, researchers, and anybody else who has an interest in the inner workings of life are the target audience for this kind of instruction since it is designed to gradually expand knowledge, beginning with fundamental principles and progressing to cutting-edge study areas.

In the first few chapters of this book, the authors discus the origins of life as well as the structural and functional differences that exist between prokaryotic molecules and eukaryotic cells. By reading these chapters, you will gain detailed knowledge that lays the foundation for comprehending the fundamental ideas that underlie cellular biology generally.

After that, we will dig into the primary organelles that are responsible for defining the architecture and function of the cell. In each chapter, an essential component is discussed, including the nucleus, the endoplasmic reticulum, the Golgi apparatus, ribosomes, lysosomes, vacuoles, and plasma membranes. As the reader progresses through these chapters, they will get a comprehensive understanding of how the complex machinery of the cell works in harmony to maintain life forms. After that, we move on to semi-autonomous organelles like mitochondria and chloroplasts, focusing on the distinct functions that these organelles play in the generation of energy and the activities of the metabolic system. The topic of discussion continues with the cytoskeletal components and molecular transport, which are responsible for the conformation, structure, and mobility of the cells within the cell.

It is essential to modern biology to have a solid understanding of cellular communication, and cell signalling and transduction are the processes that explain the intricate ways in which cells detect and react to their surroundings. Consequently, this naturally leads to the regulation of the cell cycle and the processes that regulate cell division, which is then followed by a discussion of cell death, which is an essential step for preserving homeostasis. The clinical and therapeutic aspects of the subject matter are brought into emphasis in the final chapters of the book. It is the study of cancer biology that investigates the uncontrolled development of cells and the harmful effects of this expansion. The final chapters provide an in-depth examination of the intriguing world of stem cells and cancer stem cells, discussing the therapeutic potential of these cells as well as their increasing significance in contemporary medicine.

By the time you reach the conclusion of this book, you will not only gain a profound understanding of cell biology, but you will also have insights into the most recent achievements that are affecting research and therapy. Our intention is that this book will serve as both a resource and a source of inspiration for future investigations in the field of biology.

K. N. Aruljothi
Department of Genetic Engineering
College of Engineering and Technology
SRM Institute of Science and Technology
Kattankulathur, Chengalpattu - 603203
Tamil Nadu, India

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This book represents a significant journey of learning, reflection, and progress, made possible through the invaluable support, guidance, and encouragement of numerous individuals. I wish to convey my sincere appreciation to God, my family, and my esteemed research mentors and colleagues.

I want to express my sincere gratitude to my research group, special kudos to Mr. K Kumaran, Ms. Kruthika, Ms. Sanjana D, Ms. Raksa, Ms. Srisri SK, Mr. Danyal Reyaz, Ms. Sayantani C, and Mr. Sasitharan T for their steadfast support and confidence in me. Their love, patience, and understanding during this journey have truly been invaluable to me. I appreciate your support in pursuing my dreams and the understanding you've shown in allowing me the time and space to do so.

I sincerely appreciate the invaluable editorial insights and contributions provided by my beloved associates, Dr. Satish Ramalingam, Dr. Krishnan Anand, Dr. Prakash Gangadaran, Dr. Kirubakaran Rangasamy, and Dr. Dannie Macrin. I truly appreciate their insightful suggestions, which have significantly enhanced my ideas and improved the book beyond what I could have accomplished alone.

I extend my deepest gratitude to my mentor, Prof. Devi Arikketh, whose mentorship, insightful guidance, and unwavering support were instrumental in shaping my research and personal growth.

My heartfelt thanks to my mentor, Prof. Sharon Prince, Professor and Head of the Cell Biology Division at the University of Cape Town, whose guidance and inspiration have profoundly shaped my passion and expertise in cell biology.

Finally, I would like to express my heartfelt gratitude to the Department of Genetic Engineering and SRM Institute of Science and Technology for their unwavering support and invaluable resources, which have been instrumental in the completion of this book.

List of Contributors

Abhinav Roy	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
B. Surya	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Danyal Reyaz	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Dannie Macrin	Department of Computational Biology, Institute of Bioinformatics, Saveetha School of Engineering, SIMATS Saveetha Institute of Medical and Technical Sciences, Chennai, India
Disha Kamath	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Faizaan Khan	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Gargii Chatterjee	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Harin N. Ganesh	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Janani Balaji	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Krishnan Anand	Department of Chemical Pathology, School of Pathology, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa
K.N. Aruljothi	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Kruthika Prakash	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
K. Kumaran	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Keerthana Ramesh	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Keerthivasu Ramasamy	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Lakshmi Sai Varshini Yedavalli	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Meghana A. Shakthi	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Mashira Rahman	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India

Prakash Gangadaran	Department of Nuclear Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea Cardiovascular Research Institute, Kyungpook National University, Daegu, Republic of Korea BK21 FOUR KNU Convergence Educational Program of Biomedical Sciences for Creative Future Talents, School of Medicine, Kyungpook National University, Daegu, Republic of Korea
R. Kirubakaran	Department of Biotechnology, Vinayaka Mission's Kirupananda Variyar Engineering College, Vinayaka Mission's Research Foundation-DU, Salem, Tamil Nadu, India
Ranjini Sengupta	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Raksa Arun	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Rohan Vyas	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Ramya Lakshmi Rajendran	Department of Nuclear Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea Cardiovascular Research Institute, Kyungpook National University, Daegu, Republic of Korea BK21 FOUR KNU Convergence Educational Program of Biomedical Sciences for Creative Future Talents, School of Medicine, Kyungpook National University, Daegu, Republic of Korea
Sayantani Chattopadhyay	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Soumyadeep Maiti	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Sanjana Dhayalan	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Shanmuga Priya	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
S. Sahasra	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Shalini Roy	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Sparshika Mishra	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
S. Gnanavel	Department of Biomedical Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Srisri Satishkartik	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India

S. Aswini	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Shambhavi Jha	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
S. Manvi	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Saloni Semwal	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
S. Pooja	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Satish Ramalingam	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
T. Sasitharan	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Vasanth T.L. Kanth	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Vanshikaa Karthikeyan	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India
Vedika Kartha	Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India

CHAPTER 1

Foundations of Life: Cells and Origin

Meghana A. Shakthi[1], Harin N. Ganesh[1], R. Kirubakaran[2] and **K.N. Aruljothi[1,*]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

[2] *Department of Biotechnology, Vinayaka Mission's Kirupananda Variyar Engineering College, Vinayaka Mission's Research Foundation-DU, Salem, Tamil Nadu, India*

Abstract: Various theories explain life's origin, including the Oparin-Haldane hypothesis, which suggests that life originated from simple organic molecules in Earth's early reducing atmosphere. This was also supported by the Miller-Urey experiment. The cell is the most fundamental unit of an organism. The cell theory states that all living organisms are composed of cells; an organism's basic unit is a cell, and cells arise from pre-existing cells. A basic cell consists of a nucleus, cytoplasm, cell membrane, and cell organelles. The cell organelles are suspended in the cytoplasm. Prokaryotic cells have an undefined region composed of genetic material called the nucleoid and are devoid of a membrane, unlike eukaryotes. Organelles present in all Eukaryotic cells are the Endoplasmic Reticulum, Ribosomes, Golgi Apparatus, Mitochondria, Plastids, and Vacuoles. Each organelle is specialized to function in a certain way, thereby regulating the cell's metabolism. There is a distinct difference between animal and plant cells. Some constituents are specialized for the plant cell, such as the Cell wall, Vacuoles, and the Plastids. Some are specialized for animal cells, such as Centrioles, lysosomes, Cilia, and Flagella. Cells are effectively detected, viewed, and characterized by numerous tools. The microscope plays an integral role in the world of Cell Biology. Since the invention of the standard microscope, there have been many variations to it, enhancing our ability to view microscopic structures.

Keywords: Abiogenesis, Cell organelles, Eukaryotes, Living being, Prokaryotes.

INTRODUCTION

Theory of Spontaneous Generation

An ancient theory proposed around 350 BC was widely believed until the seventeenth century. Greek Philosopher Aristotle articulated that living things could arise from non-living components. He did so by raising striking questions,

* **Corresponding author K.N. Aruljothi:** Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India; E-mail: aruljotn@srmist.edu.in

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such as how new fish are introduced in a freshly formed pond or frogs' unexpected appearance on the Nile River's banks [1]. He proposed that an organism can arise from non-living material if the material has pneuma or 'vital heat'.

For a long time, it was believed that living organisms could spontaneously arise out of their niche. It wasn't until the late 17th century that Francesco Redi, an Italian Scientist, refuted the Theory of Spontaneous Generation by providing solid proof that maggots did not appear spontaneously on a slab of rotten meat stored for days [2]. He disproved this by storing one slab in an airtight container, another in the open, and the other covered with gauze. He had observed that only that maggot arose on the uncovered meat. He later concluded maggots did not arise from the beef in the airtight contained. However, he noticed maggots on the gauze and concluded that the maggots were offspring of common flies.

Furthermore, Louis Pasteur (1859) continued to disprove the theory by boiling meat broth in a swan-necked flask. He aimed to prove that the downward curve of the flask prevents the particles from reaching the broth, hence hindering growth. When the flask was overturned, the particles could reach the broth much better, and it clouded immediately. The 'Law of Biogenesis', meaning life arises from previously existing life, had a good conclusive result, but not many favored Pasteur's findings [3].

It was not until John Tyndall's experiment in 1876 that Pasteur's conclusions were supported. Tyndall repeated Pasteur's experiments only to observe that some boiled growth media had remained sterile while others did not, despite boiling for a long time. He discovered that endospores (heat-resistant species that can develop into bacteria under favorable environmental conditions) could grow on a nutrient medium, posing a hindrance to arriving at an accurate conclusion [4]. Tyndall thus devised a sterile medium where even endospores could not survive, which required a series of mechanisms and steps to ensure sterility.

Abiogenesis for the Origin of Life

The notion that living organisms arose from non-living matter on Earth more than 3 billion years ago forms the backbone concept of abiogenesis. Russian biochemist Aleksandr Oparin and British scientist J.B.S. Haldane, in the 1920s, proposed individual ideas that formed a theory, and the basic outline of it is that non-living matter, with the help of an external source of energy, for example, UV radiation, can form organic molecules [5].

Oparin believed Coacervates were the precursors to the basic cell, and they may have been one of the very first entities to exhibit life-like properties, such as

growth and reproduction. Coacervates are droplet-like structures formed during liquid-liquid phase separation [6]. Oparin, backed by many other prominent scientists, firmly believes that Coacervates are the precursors of cells.

Haldane believed that simple inorganic materials formed into more complex molecules in the presence of external energy sources, such as UV radiation, over time. The combination of both notions is what laid an essential foundation for abiogenesis.

The Miller-Urey experiment performed in 1953 by American scientists Harold.C.Urey and Stanley Miller provided solid proof for the Oparin-Haldane hypothesis [7]. The scientists sealed Hydrogen, Methane, Ammonia, and water in a glass flask and generated an electrical discharge, stimulating lightning. After a week of discharging electrical sparks, it was observed that the water had turned reddish and turbid, and yellow-brown deposits were on the electrodes inside the apparatus. This indicated the synthesis of amino acids – the building blocks of protein. The groundbreaking experiment and Oparin-Haldane theory paved the way for research focused on Astrobiology- the study of life in the universe.

Cell and its Contents

Following the invention of the microscope in the 16th century, Robert Hooke, in the year 1665, observed small compartments or honeycomb-like structures and named them cells, as the cellulose walls in the cork he observed reminded him of rooms or monasteries usually occupied by monks (cellula) (Fig. **1**). The Latin word ‘cellula’ means storeroom or chamber. All of these were published in his work Micrographia [8]. These small compartments would become all living organisms' basic, functional, and structural units.

In 1674, Anton Van Leeuwenhoek seemingly observed protists and, years later, bacteria, which he termed the coin ‘animalcules,’ meaning microscopic animals [9]. This was the first instance a living cell had been discovered. French Chemist Francoise Raspail laid an essential foundation for the Cell Theory – that cells arise from pre-existing cells, which he hypothesized from witnessing binary fission, wherein a single cell divides into two daughter cells [10].

CHAPTER 2

Prokaryotes *vs.* Eukaryotes: Comparative Structural and Functional Insights

Kruthika Prakash[1], Sayantani Chattopadhyay[1], T. Sasitharan[1], Soumyadeep Maiti[1], Sanjana Dhayalan[1], K. Kumaran[1], R. Kirubakaran[2*] and **K.N. Aruljothi[1]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

[2] *Department of Biotechnology, Vinayaka Mission's Kirupananda Variyar Engineering College, Vinayaka Mission's Research Foundation-DU, Salem, Tamil Nadu, India*

Abstract: Organisms are fundamentally divided into prokaryotes and eukaryotes, except for viruses. Further classifications are depicted in various classifications, among which the most recent one is Whittaker's classification. Prokaryotes, the primitive organisms, gave rise to eukaryotes, and this transformation led to simple single-celled organisms evolving into colonies and multicellular cells. Prokaryotic cells, which include bacteria and archaea, exhibit diverse metabolic processes such as autotrophy and heterotrophy. In contrast, eukaryotic cells are characterized by the presence of a well-defined nucleus and membrane-bound organelles, unlike prokaryotic cells. In contrast, eukaryotes developed around 2 billion years ago and possess complex cellular structures, including a well-defined nucleus and various organelles, such as mitochondria and chloroplasts. The transition from unicellular to multicellular life is a significant evolutionary milestone that involves various adaptations and mechanisms, including cell-to-cell communication, adhesion, and coordinated growth. Genetic conservation and epigenetic mechanisms play pivotal roles in the development of multicellular structures, as demonstrated in organisms like fungi and metazoans. Eukaryotic cells, such as those from yeast and mammalian sources, are pivotal in biotechnological applications, including the production of recombinant proteins and gene therapy. Their ability to properly fold and process proteins allows for the creation of functional biopharmaceuticals and vaccines that simulate pathogen structures to invoke robust immune responses. Notable eukaryotic microorganisms like algae and fungi are also increasingly recognized for their potential in sustainable biofuel production. Since genes serve as the backbone for almost all cells, they can be manipulated to be more user-friendly.

* **Corresponding author R. Kirubakaran:** Department of Biotechnology, Vinayaka Mission's Kirupananda Variyar Engineering College, Vinayaka Mission's Research Foundation-DU, Salem, Tamil Nadu, India; Tel: 9095288654; E-mail: rangasamykirubakaran@gmail.com

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Keywords: Biofuel production, Characteristics, Eukaryotes, Evolution, Evolutionary biology, Gene therapy, Genes, Multicellularity, Prokaryotes, Recombinant proteins, Whittaker's classification.

INTRODUCTION TO PROKARYOTES

With a simpler cell structure than eukaryotes, prokaryotes are unicellular creatures devoid of membrane-bound organelles or a nucleus; their genetic material is arranged in a single circular DNA molecule that floats freely inside the cell. Common examples of prokaryotes, bacteria, and archaea lack compartmentalization, which helps them to adapt and flourish in many habitats, as shown in Fig. **1**. Among the first living entities on Earth, prokaryotes have greatly affected metabolic reactions, forming the ecosystems of the planet [1]. Originally discovered in the late 17th century with the development of the microscope, Dutch scientist Antonie van Leeuwenhoek saw "animalcules"—microbes—in 1676, hence establishing the basis for microbiology [2]. While Carl Woese's genetic categorization in the 1970s separated Archaea from Bacteria, redefining our knowledge of prokaryotes, advances in staining and microscopy techniques helped scientists like Louis Pasteur and Robert Koch identify bacteria as agents of illness.

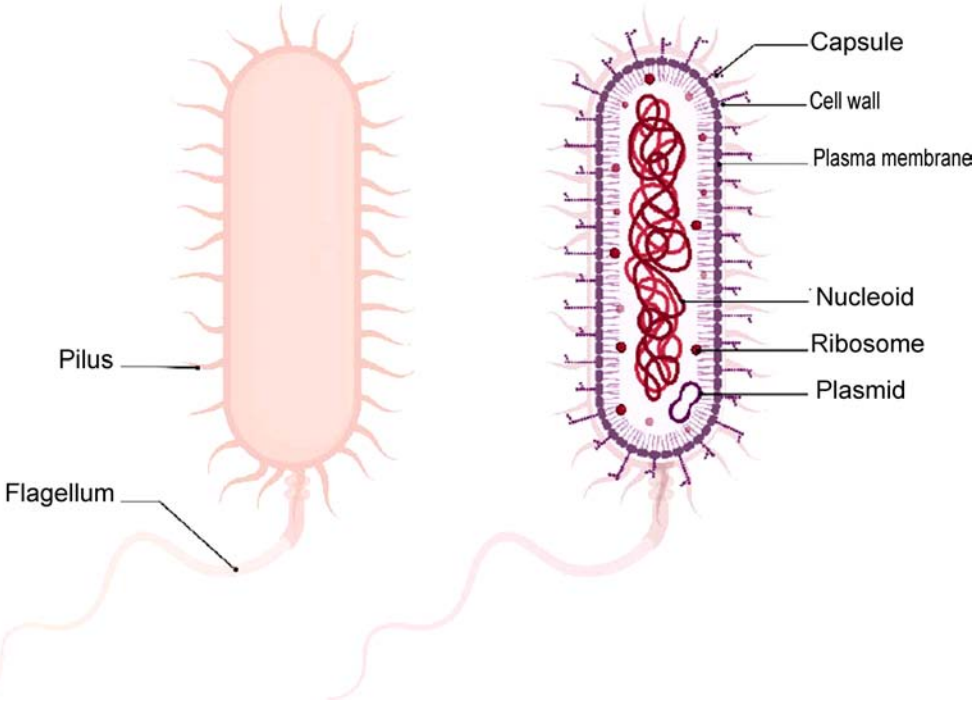

Fig. (1). Bacterium, a prokaryote

Crucially for plant development, prokaryotes drive biogeochemical cycles that help break down organic matter and recycle nutrients and nitrogen fixation, supporting ecosystems. Beyond their function in the surroundings, prokaryotes are essential for human life since they help digestion and enable waste breakdown and fermenting [3]. With their research opening the path for industrial uses, bioremediation, and genetic engineering, they also synthesize vitamins, antibiotics, and other chemicals, thereby stressing the need for prokaryotes to maintain the environment and improve health and quality of life.

Prokaryotic Diversity

Prokaryotes exhibit different forms, structures, metabolic pathways, and ecological responsibilities among their tremendous and varied diversity. Their adaptability lets them live practically anywhere on Earth, from human bodies to deep waters. Their taxonomy, form, metabolic strategies, and ecological niches are examined here.

Classification of Prokaryotes

Separated by genetic, biochemical, and physiological traits, bacteria and Archaea represent the two main domains of prokaryotes. Among the most well-known prokaryotes—from helpful gut microorganisms to disease-causing pathogens—are bacteria [4]. Living in almost every environment on Earth, they are pretty varied and have cell walls typically made of peptidoglycan, a unique polymer providing structural support. Previously believed to be bacteria, Carl Woese identified archaea as a discrete domain based on their distinct genetic and metabolic properties. Like bacteria, Archaea can survive in hostile conditions because their cell membranes consist of ether-linked lipids rather than ester-linked lipids. Usually, extremophiles survive in hot springs, salt flats, and deep-sea vents. Archaea can also be found in more common environments like the human intestine [5].

Morphological Diversity

The range of forms, sizes, and configurations that prokaryotes exhibit enhances their adaptability and usefulness in many contexts. Among the most often occurring forms are cocci (spherical-shaped bacteria such as *Streptococcus*), bacilli (rod-shaped cells like *Escherichia coli*), *spirilla* (spiral-shaped cells like *Spirillum*), and vibrios (comma-shaped cells like *Vibrio cholerae*). Usually small, ranging from 0.2 to 5 micrometers, prokaryotic cells can vary in size depending on their environment and genes. Division patterns affect their cellular structures as well; they produce linear chains (as seen in streptococci), grape-like clusters

CHAPTER 3

Nucleus: the Control Centre of the Cell

K. Kumaran[1], Harin N. Ganesh[1] and **K.N. Aruljothi[1,*]**

[1] Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India

Abstract: The nucleus is a crucial organelle in eukaryotic cells, serving as the primary center for genetic material and essential cellular processes like replication, transcription, and gene expression. The nucleus, surrounded by a double-membrane nuclear envelope, includes critical elements like chromatin, the nucleolus, and nuclear pore complexes, each integral to functions such as gene expression, RNA processing, and ribosome assembly. This document offers a comprehensive examination of nuclear structure and its functional dynamics, highlighting the importance of Cajal bodies in RNA metabolism and the influence of nuclear organization on gene regulation. Furthermore, it underscores the consequences of nuclear irregularities in several illnesses, such as laminopathies and chromatin remodeling disorders, which may have significant health ramifications. As research advances, novel treatment methods aimed at nuclear functions, including gene editing technologies and techniques for treating laminopathies, are becoming increasingly prominent. These observations highlight the nucleus's essential function in preserving cellular integrity and operation and its significance in health and disease management.

Keywords: Cajal bodies, CRISPR-Cas9, DNA replication, Eukaryotic cells, Gene expression, Genetic material, Hutchison-Gilford Progeria Syndrome, laminopathies, nuclear matrix, nuclear pore complexes, RNA processing, Spinal muscular atrophy, Treacher Collins Syndrome.

INTRODUCTION

The nucleus is a membrane-bound organelle that acts as the command center of eukaryotic cells, ensuring genetic information integrity and controlling cellular activity. It is usually the most visible organelle in the cell, occupying a large percentage of the cellular volume. Gene expression, DNA replication, and cell division occur exclusively because of the eukaryotic cell's nucleus. In the prokaryotes, a nucleoid is present instead of a nucleus. The genetic material known as DNA (deoxyribonucleic acid) will be present as chromatin, a mixture of

* **Corresponding author K.N. Aruljothi:** Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India; E-mail: aruljotn@srmist.edu.in

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proteins and DNA that is arranged into chromosomes during cell division. The DNA that codes for everything from protein synthesis to cell growth and reproduction is found in the nucleus in eukaryotes / nucleoid in prokaryotes and includes all the instructions for the cell to function. Despite the more straightforward organization of genetic material, prokaryotes effectively regulate gene expression and adapt rapidly to environmental changes. Their streamlined genome organization and mechanisms, like operons (clusters of genes under a single promoter), enable efficient and coordinated gene expression. This efficiency contributes to their high adaptability and survival across diverse environments. At the same time, eukaryotic cells have a highly organized nucleus with complex DNA packaging that facilitates intricate regulation of gene expression and cellular specialization. In contrast, prokaryotic cells lacking a defined nucleus possess a more straightforward yet efficient system of DNA organization that supports rapid growth and adaptability. The presence of a membrane-bound nucleus is the characteristic that sets eukaryotic cells apart from prokaryotic cells, which have genetic material distributed throughout the cytoplasm and no clearly defined nucleus [1].

History

Over the decades, the discovery and comprehension of the nucleus have undergone substantial changes, playing a pivotal role in advancing cell biology. Robert Brown, a Scottish botanist, coined the term “nucleus” for the first time in a biological context in 1831. Brown saw a tiny, thick, spherical structure inside the cells of orchids and other plants while investigating plant cells under a microscope. He called this structure the “nucleus,” which is Latin for “kernel” or “core.” Though Brown did not wholly comprehend its purpose then, he recognized it as a recurring and essential aspect of the cell. In the years that followed, many scientists verified Brown's findings and started to make assumptions regarding the function of the nucleus. Matthias Schleiden and Theodor Schwann contributed to the cell theory in the middle of the 19th century. This theory postulated that all living things comprise cells, with the nucleus considered a crucial component [2].

Expanding on this idea, Rudolf Virchow proposed in 1855 that all cells originate from pre-existing cells, highlighting the significance of the nucleus in cell division and inheritance. Improvements in staining methods and microscopy during the late 19th century gave scientists a better understanding of the nucleus. Walther Flemming's 1880s discovery of chromosomes inside the nucleus demonstrated their function in mitosis or cell division. Later, August Weismann put out the theory that the nucleus contained genetic material, which impacted the field of genetics. Thomas Hunt Morgan and his associates' work showed that

genes found on chromosomes inside the nucleus were the units of heredity, significantly advancing our knowledge of the function of the nucleus in the early 20th century. This discovery confirmed the nucleus's function in genetic information storage and inheritance [3]. The nucleus's function as the cell's command center was further demonstrated in 1953 with the discovery of the DNA structure by James Watson and Francis Crick. It was discovered that DNA, which is found in the nucleus of eukaryotic cells, is the molecule in charge of storing and transferring genetic information. This discovery made modern molecular biology possible by establishing the nucleus as the primary locus of gene control, replication, and expression [4].

STRUCTURE AND FUNCTION

Structure of Nucleus in Eukaryotes

The nucleus comprises several parts that form a highly ordered structure supporting its role as the cell's command center. The nuclear envelope is a two-layered barrier that surrounds the cell nucleus and keeps it separate from the cytoplasm. This envelope consists of an inner and outer membrane, both lipid bilayers. The outer membrane is continuous with the endoplasmic reticulum, facilitating the transport of materials between the nucleus and cytoplasm. Nuclear pores are embedded within the nuclear envelope, which regulate the passage of molecules such as nucleic acids and proteins into and out of the nucleus. A gel-like substance fills the nuclear space inside the nucleoplasm, providing structural support and a medium for suspending various nuclear components. Among these components, chromatin, a complex of DNA and proteins, plays a crucial role in packaging genetic material and regulating gene expression. Another vital structure within the nucleoplasm is the nucleolus, a dense, spherical body primarily responsible for producing and assembling ribosomes (Fig. **1**) [1].

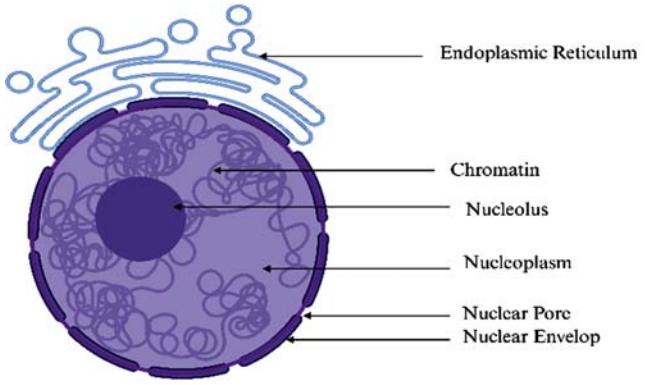

Fig. (1). Structure of the nucleus in eukaryotes.

CHAPTER 4

Endoplasmic Reticulum: The Cellular Factory

Shanmuga Priya[1], K. Kumaran[1], Sanjana Dhayalan[1], Krishnan Anand[2,*] and **K.N. Aruljothi[1]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

[2] *Department of Chemical Pathology, School of Pathology, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa*

Abstract: The endoplasmic reticulum is an organelle that performs dynamic functions in many critical cellular processes. This chapter discusses the evolutionary aspects of the Smooth ER (SER), the tasks of RER, their involvement in cellular stress responses, and implications for human health and disease. Complexities of ER stress and their relationship to conditions such as ulcerative colitis and type 2 diabetes will be discussed. The chapter discusses the therapeutic potential of targeting ER stress pathways as therapy for UC. We also discuss the relationship between the ER and autophagy, a cellular degradation and recycling process. Discussion is taken upon the role of the mitochondria-associated ER membrane (MAM) in calcium signaling and its implications for various cellular processes. This chapter summarizes the roles of ER, trying to unveil the complexity of the ER functions and the importance of the ER in both human health and disease.

Keywords: Apoptosis, Autophagy, Endoplasmic Reticulum, ER Stress, Glycosylation, Homeostasis, Lipid Synthesis, Mitochondria, Mitochondria-Associated ER Membrane (MAM), Protein Folding, Quality Control, Smooth ER, Type 2 Diabetes, Ulcerative Colitis.

INTRODUCTION

The endoplasmic reticulum encompasses a membrane-bound organelle with the framework of a network of sacs and tubules. It is continuous with the nuclear envelope. The ER is vital in shipping the synthesized proteins to the Golgi apparatus for further processing. Apart from synthesizing proteins, the ER synthesizes the lipids that essentially serve as the membrane in all organisms. The endoplasmic reticulum can be classified into two types based on the compounds they synthesize: Smooth Endoplasmic Reticulum (SER) and Rough Endoplasmic

* **Corresponding author Krishnan Anand:** Department of Chemical Pathology, School of Pathology, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa; E-mail: organicanand@gmail.com

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Reticulum (RER). The Rough ER has attached ribosomes that help in protein synthesis. Smooth ER lacks ribosomes, which are key drivers in protein synthesis. Therefore, the SER is involved in the production of lipids, and the RER plays a role in Protein synthesis. Apart from synthesizing proteins and lipids, the ER plays other vital roles in transporting proteins and lipids, storing Ca^{2+} ions, steroid production, stress regulation mechanisms (endoplasmic reticulum stress), and protein folding machinery [1]. Fig. (**1**), below, denotes the structural orientation of the endoplasmic reticulum. Rough ER has ribosomes on its surface, whereas smooth endoplasmic reticulum lacks ribosomes.

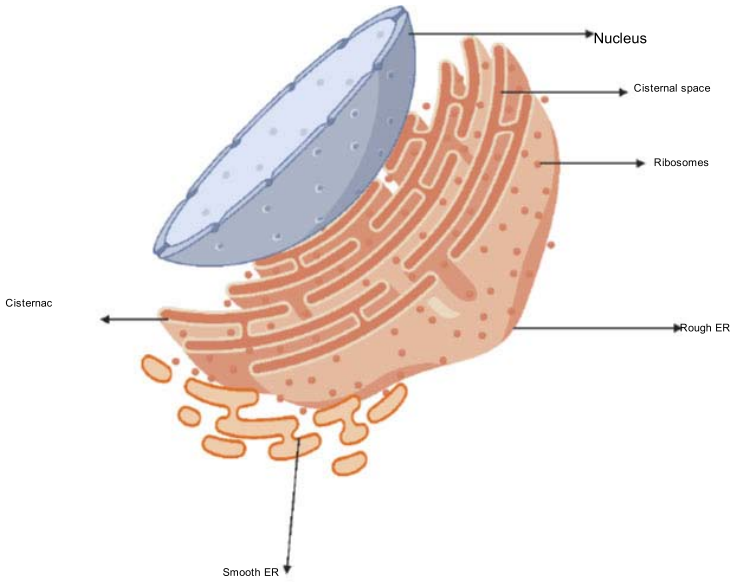

Fig. (1). Structural orientation of endoplasmic reticulum.

FUNCTIONS OF RER

The protein translocation in the RER occurs in two ways,

1. Where the protein, while being synthesized by the ribosomes, undergoes the translocation and translation simultaneously in ER, called the co-translational translocation.
2. The proteins synthesized by the free ribosomes are translocated into the ER using the SEC pathway.

The ER synthesizes three significant proteins: secretory proteins, integral membrane proteins, and Lumenal resident proteins. The secretory proteins are involved in folding proteins and delivering specific proteins. The integral

membrane proteins are derived from the ER, and almost 30% of the entire human genome codes for the integral membrane proteins. The last category of proteins is called the luminal resident proteins of the ER, Golgi, Nuclear envelope, and Lysosomes. Therefore, RER plays a significant role in the biosynthesis of proteins. An example of the integral membrane protein is Single Carboxy-terminal TM spans (tail-anchored membrane proteins*)*. Most organelles' protein requisite are satisfied by the protein synthesis at the RER. Therefore, molecules for protein synthesis must reach the ER for processing, followed by proper folding. The protein folding machinery folds the protein synthesized by the ribosomes at the RER, called the chaperones. Folding is essential for building a fully structural and functional unit of protein. Therefore, proteins reach a thermodynamically stable state. Also, proteins are not independent in their functioning. Their interactions can range from short and temporary within their functional group to stable oligomers in biological synthesis. The majority of proteins in the secretory pathway include oligomers. Therefore, the proteins must be folded at the late translational steps [2].

The Process of Protein Folding Associated with Molecular Chaperones

The chaperon-assisted protein folding is followed by the assembly of multi-subunit proteins, formation of the disulfide bond, and N-glycosylation (initial stages); in the case of the proteins of the plasma membrane, glycolipid anchors are added to the proteins. The Lumenal proteins in the ER play the primary role in assisting the folding of proteins and assembly of the polypeptide units that are newly translocated. The molecular chaperones, being proteins, act on a non-native protein to stabilize or bring about its native conformation. These molecular chaperones do not appear in the final three-dimensional confirmation of the proteins. The major ER resident chaperones are Hsp70 Bip, lectin chaperones like calnexin, and calreticulin (folding glycoproteins). Bip releases the abnormally folded proteins, which are then removed from the ER by the Endoplasmic reticulum-associated degradation process [3]. In the process of N-glycosylation, asparagine residues of proteins are glycosylated that are present within the ER. By this time, the translation is still in process (co-translational). In the first step, the oligosaccharides with 14 sugar residues are added to the acceptor molecules of protein, that is, the asparagine residue. The lipid carrier dolichol is the site for synthesizing the oligosaccharide anchored to the ER membrane. From here, the oligosaccharide unit is transferred to the asparagine residues by an enzyme associated with a membrane called the oligosaccharide transferase. Three glucose units are removed from the long oligosaccharide, and the protein remains in the endoplasmic reticulum. As discussed earlier, the protein from the ER has to reach the Golgi apparatus for further modification, packing, and shipping. Glycosylation is significant as it provides signals to promote protein folding, followed by

CHAPTER 5

Golgi Apparatus: Shaping and Shipping Cellular Proteins

S. Sahasra[1], Sanjana Dhayalan[1], K. Kumaran[1] and **K.N. Aruljothi[1,*]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

Abstract: The Golgi body is an organelle in charge of altering proteins and lipids after translation and getting them ready for transport to spots within and outside the cell. This part of our study investigates its makeup, focusing on three key sections— cis side, middle section, and trans side, and how they contribute to sugar attachment to proteins, lipid processing, and protein arrangement. Furthermore, the chapter discusses how it plays a role in cell functions like secretion and creating lysosomes, and its impact on diseases like neurodegenerative conditions, infections, and cancer. It also covers progress in treatments and research related to the Golgi apparatus, including its involvement in the dynamics of COVID-19.

Keywords: Cancer, Cisternae, COVID-19, Golgi Apparatus, Lysosome Formation, Neurodegenerative Diseases, Phosphorylation, Post-Translational Modification, Protein Sorting, RAB GTPase, Sphingomyelin, TGN (Trans Golgi Network), A-Synuclein.

INTRODUCTION

The Golgi apparatus is a fundamental organelle and a key feature of eukaryotic cells that distinguishes them from prokaryotes. It consists of membrane-bound vesicles attached to stacked, flattened sacs known as cisternae. It helps in the post-translational modification and sorting of proteins and lipids. It packages these modified molecules into vesicles, which are then transported to specific locations inside and outside the cell through endocytic and exocytic pathways. As a result, it is vital for preserving cellular homeostasis and facilitating proper cell functions, making it crucial for intracellular transport and protein secretion. The Golgi apparatus can be traced back to the Last Eukaryotic Cell Ancestor (LECA), implying that the presence of the Golgi is nearly two billion years old, originating around the time of the divergence of major eukaryotic lineages [1]. The endosym-

* **Corresponding author K.N. Aruljothi:** Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India; E-mail: aruljotn@srmist.edu.in

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biotic theory has been turned down, and the trending view is that the Golgi and other organelles of the endomembrane system evolved through autogenous means, meaning that they originated from inside the cell and not from endosymbiosis. Functional diversity exists in the different eukaryotes, from the ring Golgi in the malaria parasite to the mobile Golgi in the plants. This merely underlines the functional plasticity of the Golgi and its adaptation to various ecological niches.

STRUCTURE OF GOLGI APPARATUS

It is worth noting that the early description of the Golgi apparatus was "apparato reticulare interno", meaning the internal reticular apparatus was based on its morphology. It is a membrane-bound organelle, made of a series of cisternae. These stacks often appear as a series of flattened pancakes or discs. The size of the Golgi stacks can differ, with each stack containing a variable number of cisternae. These stacks are encircled by a network of vesicles and tubules, which are essential for the transport of materials to and from the Golgi apparatus.

The Golgi apparatus has three compartments, called "cis", "medial," and "trans". The cis compartment is the cisternae near the Endoplasmic Reticulum (ER), the medial compartment is the central layers of cisternae, and the trans compartment is the cisternae farthest from the ER. There are two Golgi networks, which are the Cis Golgi network and the Trans Golgi network; these comprise the outermost cisternae located at the cis and trans faces of the Golgi, respectively. These networks are responsible for sorting the proteins and the lipids that are received at the cis face from the ER and released at the trans face by the Golgi (Fig. **1**).

CIS Face

The cis face in the Golgi apparatus is closest to the ER. It is located to facilitate the transfer of the newly synthesized protein and lipids from the ER. Its primary function is to receive materials (protein and lipid) that need to be processed in the Golgi apparatus. It also initiates modification of the incoming molecules, like glycosylation, sulfation, and phosphorylation. It recognizes the specific signals on the incoming molecules, which decides its destination within the Golgi stacks, thus it is the "receiving a sorting hub" of the organelle. The Golgi apparatus consists of stacked cisternae linked by tubular structures, forming a network referred to as the Golgi ribbon. At the entrance of the Golgi, known as the cis-Golgi, Vesicular Tubular Clusters (VTCs) act as a transitional area between the endoplasmic reticulum and the stacked cisternae [2].

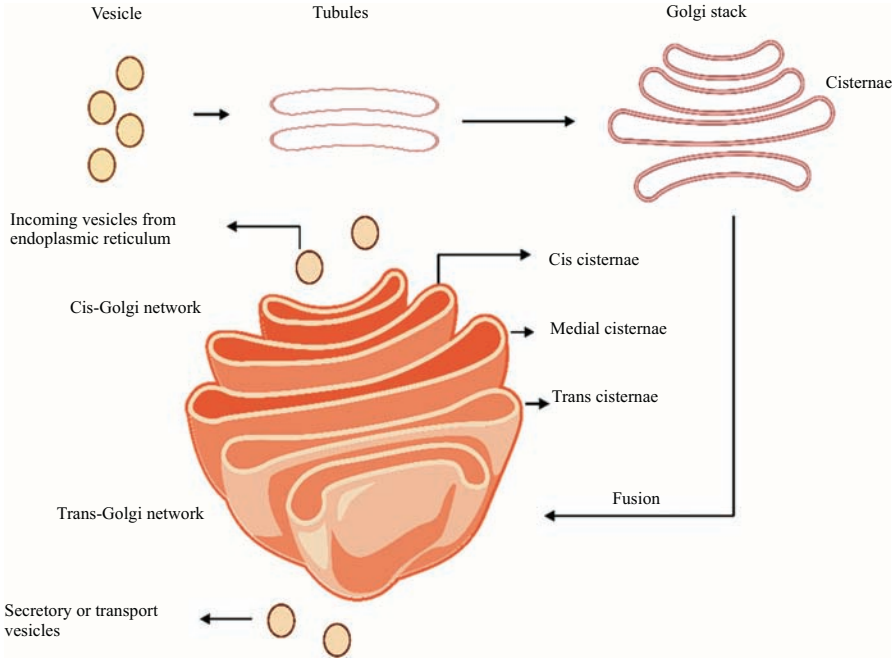

Fig. (1). The Golgi apparatus is composed of stacked cisternae interconnected by tubules, receiving vesicles from the endoplasmic reticulum and sorting proteins for their final destinations.

MEDIAL Face

The medial face is positioned between the cis face and the trans face within the Golgi stacks. The primary role of the medial face is to modify proteins and lipids. It is at this stage that many post-translational modifications occur, including glycosylation (addition of sugar molecules), sulfation, and phosphorylation, which are crucial for the functional maturation of proteins and the alteration of lipid molecules. The medial cisternae contain various enzymes that facilitate these modifications. It also helps in pH regulation within the cisternae, which is crucial for the functioning of the enzymes involved in various modifications. The medial face is responsible for further processing materials destined for secretory vesicles that will carry proteins and lipids to the cell membrane or for the formation of lysosomes, which contain enzymes for breaking down cellular waste.

TRANS Face

The trans face is positioned at the opposite end of the Golgi apparatus from the cis face and is called the “shipping” face, as it is responsible for directing modified molecules to their final destinations within or outside the cell. The primary role of the trans face is to sort out the proteins and lipids that have undergone

CHAPTER 6

Ribosomes: Engines of Protein Synthesis

Sanjana Dhayalan[1], Shalini Roy[1], K. Kumaran[1] and **K.N. Aruljothi[1,*]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

Abstract: Ribosomes are essential macromolecular complexes that translate genetic information from mRNA into proteins. Composed of rRNA and ribosomal proteins, they consist of two subunits, large and small, in both prokaryotic (70S) and eukaryotic (80S) cells, with structural differences reflecting their evolutionary adaptations. Ribosome biogenesis (Ribi) is a tightly regulated process initiated by rDNA transcription and subunit assembly in eukaryotes and involving factors like NusA and NusG in prokaryotes. Ribosomes drive protein synthesis through complex processes of initiation, elongation, termination, and recycling, facilitated by GTPases and elongation factors, ribosomopathies cause diseases such as Diamond-Blackfan Anemia and Shwachman-Diamond Syndrome, linked to mutations in ribosomal proteins. Ribosomal dysfuntion can lead to both hypo- and hyper-proliferation, increasing cancer risk. Recent advances in targeting ribosome-related pathways, such as mTORC1 inhibition, and techniques like ribosome profiling have provided insights into diseases like leukemia and medulloblastoma, revealing non-canonical ORF translation and novel therapeutic targets. These findings highlight the therapeutic potential of modulating ribosome function in disease treatment.

Keywords: ABCE1, Biogenesis, Cancer, Elongation, Eukaryotes, Fingerprinting, GTPases, Prokaryotes, Protein Synthesis, Ribosomal Subunits, Ribosome Profiling, Ribosomopathies, rRNA, Termination, tRNA.

INTRODUCTION

Ribosomes are essential cellular organelles found in all living organisms, serving as the molecular machinery responsible for protein synthesis, a fundamental biological process. These intricate macromolecular complexes comprise ribosomal RNA (rRNA) and ribosomal proteins; they are essential for converting genetic information from messenger RNA (mRNA) into polypeptide chains, which fold into valuable proteins. These indispensable organelles play a central role in synthesizing proteins, which are vital for the structure and function of all

* **Corresponding author K.N. Aruljothi:** Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India; E-mail: aruljotn@srmist.edu.in

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living organisms. Their intricate composition and sophisticated mechanisms underscore the complexity of cellular processes and the evolutionary significance of protein synthesis. The ribosomal function provides insight into fundamental biological processes and has implications for medical research, particularly in developing antibiotics that target bacterial ribosomes without affecting eukaryotic cells. Ribosomes are categorized into two primary types based on cellular organization: prokaryotic and eukaryotic ribosomes. Despite their differences, both types share a similar functional architecture. The structural differences between prokaryotic and eukaryotic ribosomes are significant, particularly in the size and composition of the rRNA and protein components [1].

Ribosome in Prokaryotes and Eukaryotes

In eukaryotic cells, ribosomes include two distinct subunits: the large ribosomal subunit (60S) and the small ribosomal subunit (40S). The 60S subunit comprises three rRNA molecules: 5S, 5.8S, 25S/28S rRNA, and 46 associated ribosomal proteins. The small 40S subunit contains a single rRNA molecule, the 18S rRNA, associated with 32 ribosomal proteins. The highly regulated process of ribosomal component assembly takes place in the nucleolus, where mature ribosomal subunits are formed by the combination of ribosomal proteins and rRNA transcription [2]. Prokaryotic ribosomes in organisms such as bacteria are slightly smaller than their eukaryotic counterparts. They consist of a 50S subunit and a 30S subunit. 34 proteins and 5S and 23S rRNA are found in the 50S subunit, whereas 21 proteins and 16S rRNA are found in the 30S subunit.

The protein synthesis, or translation, involves several key steps and the coordinated action of both ribosomal subunits [3]. The small ribosomal subunit first attaches itself to the mRNA molecule and searches for the start codon. The assembly of the ribosomal subunits—40S and 60S in eukaryotes, 30S and 50S in prokaryotes—around the mRNA molecule is the first step in the translation process. In eukaryotes, the initiator tRNA, which carries methionine (Met-tRNAi), and the small 40S ribosomal subunit work together to scan the messenger RNA (mRNA) for the start codon (AUG). The big 60S subunit joins the complex upon identification of the start codon, completing the formation of the 80S ribosome.

The Shine-Dalgarno sequence on the mRNA is bound by the 30S subunit in prokaryotes, and the 50S subunit then joins to form the 70S ribosome. The large and tiny subunits join forces upon identification of the start codon to produce a functional ribosome that can synthesize proteins.

During translation, the ribosome facilitates the decoding of the mRNA sequence into a corresponding amino acid sequence. The primary function of the small

subunit is to decode the messenger RNA (mRNA) and guarantee that the appropriate transfer RNA (tRNA) molecules, each containing a distinct amino acid, are introduced into the ribosomal A (aminoacyl) site. Through its peptidyl transferase activity, the larger subunit facilitates the creation of peptide bonds between neighbouring amino acids once the proper tRNA has been positioned. The elongation of the developing polypeptide chain depends on this enzyme action. The tRNA molecules are successively added as the ribosome translocates along the mRNA. When the expanding polypeptide chain reaches a stop codon, it is released from the ribosome, indicating that translation has stopped. The completed polypeptide then undergoes folding and post-translational modifications to achieve its final functional conformation.

In eukaryotic cells, ribosomes are crucial for protein synthesis and can be found in several distinct locations, each serving specific functions. They exist in two primary forms: freely floating in the cytoplasm, referred to as cytoribosomes, or attached to the outer surface of the Rough Endoplasmic Reticulum (RER), thereby forming the rough ER. This association with the RER is significant as it facilitates the co-translational translocation of nascent polypeptide chains into the lumen of the endoplasmic reticulum. Once inside the ER, these polypeptides undergo further modifications, such as glycosylation and folding, before being trafficked to their final destinations within or outside the cell. Additionally, ribosomes are present in the stroma of plastids, such as chloroplasts, and within the mitochondrial matrix. In these organelles, ribosomes synthesize proteins encoded by their respective organellar genomes, which are distinct from nuclear DNA. This unique feature underscores the endosymbiotic theory, suggesting that mitochondria and plastids originated from ancestral prokaryotic cells. In contrast, prokaryotic cells, which lack membrane-bound organelles, exhibit a simpler ribosomal distribution. Ribosomes in prokaryotes are freely distributed throughout the cytoplasm. These ribosomes, typically smaller than their eukaryotic counterparts, are involved in translating mRNA into proteins directly within the cytoplasmic environment. This structural simplicity allows for rapid protein synthesis, which is essential for the adaptability and survival of prokaryotic organisms in diverse environments. The localization of ribosomes in eukaryotic and prokaryotic cells reflects their essential roles in protein synthesis, with distinct adaptations that facilitate cellular functions and processes.

Origin and Evolution of the Ribosome

The origins of ribosomes can be traced back to the early Earth, approximately 4 billion years ago, when the first molecules of life began to form. It is widely accepted that simple RNA molecules, capable of catalyzing chemical reactions, played a crucial role in the emergence of life. This concept is often referred to as

CHAPTER 7

Lysosomes: The Cell's Digestive System

B. Surya[1], Faizaan Khan[1], Abhinav Roy[1], Sanjana Dhayalan[1], K. Kumaran[1], Krishnan Anand[2] and **K.N. Aruljothi[1,*]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

[2] *Department of Chemical Pathology, School of Pathology, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa*

Abstract: Lysosomes serve as essential organelles in eukaryotic cells, facilitating the recycling and degradation of cellular waste through the action of hydrolytic enzymes. This acidic organelle engages with various vesicles, such as phagosomes and endosomes, to dismantle biomolecules encompassing proteins, lipids, and nucleic acids. Recent studies have illuminated the function of lysosomes in autophagy, a process wherein they contribute to the degradation of cellular constituents in response to stress or periods of starvation. Three main types of autophagic processes, macroautophagy, microautophagy, and chaperone-mediated autophagy, use central mechanisms that help the trafficking of their selective cargo. The activity of lysosomes is connected with several diseases: lysosomal storage diseases, Parkinson's disease, and muscular dystrophy are generally caused by either a lack of efficiency of the autophagosome and lysosome fusion or impairment of lysosome digestion. Mechanisms of lysosomal regeneration involve Autophagic Lysosome Reformation (ALR) and Endocytic Lysosome Reformation (ELR), with the presence of essential functions to maintain lysosomal function. Further knowledge about such processes may allow for the creation of therapies for neurodegenerative and muscular disorders characterized by a significant contribution of lysosomal dysfunction.

Keywords: Acidification, Autophagosome, Autophagy, Endocytosis, Endosomes, Hydrolytic Enzymes, Lysosomal Dysfunction, Lysosomes, Lysosomal Membrane Proteins, Neurodegeneration, Phagocytosis, SNARE Proteins..

INTRODUCTION

Commonly known as suicide bags, they are cell organelles in Eukaryotic cells that help break down and recycle waste products from the cell. Lysosomes have hydrolytic enzymes that help break down biomolecules. Some of those hydrolytic

* **Corresponding author K.N. Aruljothi:** Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India; E-mail: aruljotn@srmist.edu.in

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enzymes include Proteases, Lipases, Nucleases, and Glycosidases. Due to these enzymes, the lysosome has an acidic pH of about 5, and the pH of the cytoplasm is neutral (7.2 to 7.8); the lysosome's membrane separates both. We currently understand lysosomes as a very varied group of organelles that vary in location, acidity, functions, and the hybrid organelles they create through fusion/fission and "kiss and run" processes. Endolysosomes, phagolysosomes, autolysosomes, and other terms are used to identify different lysosomal compartments. For example, endolysosomes are intermediate compartments formed during the fusion of endosomes and lysosomes, and they are typically acidic.

Phagolysosomes form when phagosomes fuse with lysosomes to degrade engulfed particles. Autolysosomes result from the fusion of autophagosomes with lysosomes during autophagy. There's also a distinction between acidic lysosomes (like endolysosomes, which actively degrade material) and non-acidic compartments (such as terminal lysosomes), which have completed their digestive function [1, 2].

Discovery of Lysosomes

During the 1950s, de Duve *et al*. from the University of Louvain in Belgium wanted to know how insulin acts in liver cells. They wanted to find where the glucose-6-phosphatase enzyme resides, which regulates blood sugar. They added rat liver debris to distilled water and centrifuged it. They found the enzyme with high activity, but when they purified the enzyme from the cell extracts, they could not precipitate it; however, they could not dissolve it again [3]. The strategy they used was a more advanced differential centrifugation that separates cell constituents based on size and density. They lysed the liver cells, fractioned them in a sucrose medium, and assayed glucose-6-phosphatase activity in the microsomal fraction. Differential centrifugation led them to the conclusion that the activity of the control enzyme, acid phosphatase, was only 10% of what it should have been. One of the scientists kept some of the fractioned samples in the fridge for five days (Fig. **1**). On the other hand, when assaying the phosphatase activity, it was found to be equal to that which was expected. De Duve and his co-workers then hypothesized that a membrane could limit the access of an enzyme to its substrate, and resting the samples would give the enzymes time to become accessible. To these membrane-bound sacs containing acid phosphatase along with other lytic enzymes, de Duve gave the name "lysosomes" [4]. An acceptance of the discovery of lysosomes came when Christian de Duve was awarded the Nobel Prize in Physiology or Medicine in 1974. That same year, Alex Novikoff of the University of Vermont paid a visit to de Duve's laboratory. As an expert microscopist, Novikoff took the first electron micrographs of this newly discovered organelle from partially purified samples of the lysosome. The vital

role of lysosomes, for instance, was discovered by the work of Werner Strauss and his laboratory [2]. Strauss sought to determine how cells can draw molecules from outside their boundary wall through a so-called endocytosis process. He tagged proteins, followed their movement within cells, and found that protein fragments are engulfed in lysosomes. He concluded that lysosomes break down proteins.

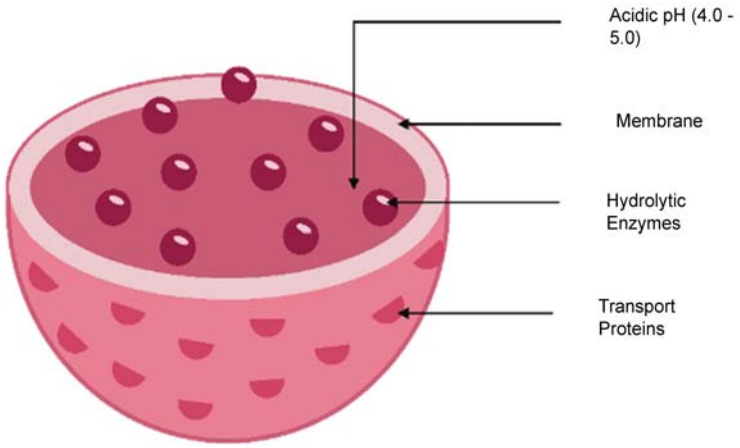

Fig. (1). Lysosome structure showing its membrane, digestive enzymes, and organelles involved in cellular degradation and recycling.

In other experiments, Zanvil Cohn incubated radiolabeled bacteria with macrophages and found that the different components of bacteria, including lipids, carbohydrates, and amino acids, were concentrated in lysosomes. Cohn deduced that lysosomes are the digestive organs of the cell, disposing of materials not produced by the cell itself and cellular products. Thus, lysosomes can be regarded as recycling stations that aid in cellular waste disposal and recycling of material ends [5].

Evolution of Lysosomes

Lysosomes are formed when vesicles from the Golgi Complex fuse with endosomes. Endocytosis is a process in which a section of the plasma membrane pinches off to form vesicles known as endosomes (Fig. **2**) [5].

CHAPTER 8

Vacuoles: The Storage Vaults of the Cell

S. Sahasra[1], S. Aswini[1], K. Kumaran[1], Sanjana Dhayalan[1] and **K.N. Aruljothi[1,*]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

Abstract: Vacuoles are cell structures enclosed in membranes that play roles in various cellular functions within plant cells, some animal cells, and fungi cells. This section delves into the array of duties that vacuoles perform, like storing water and nutrients and aiding in maintaining turgor pressure, pH balance, and detoxification within cells. It also discusses the variations seen among organisms with a focus on specific vacuole types, including the central vacuole found in plants, the autophagic variety seen in animals, and the versatile fungal vacuoles. Furthermore, the chapter explores how vacuoles play a role in autophagy and defense mechanisms and the importance of vacuole-specific proteins such as Tonoplast Intrinsic Proteins (TIPs). It also covers progress in vacuole research, including their potential for use in drug delivery systems, enhancing plants' ability to withstand stress.

Keywords: Abscisic Acid, Autophagy, Cellular Detoxification, Glycerol, Fungal Vacuole, Ion Regulation, Membrane, Nutrients, Osmoregulation, Plant Vacuole, Tonoplast, Tonoplast Intrinsic Proteins (TIPs), Turgor Pressure, Vacuolar pH..

INTRODUCTION

Vacuoles are membrane-bound organelles found primarily in plant and fungal cells and some animal cells. In animal cells, vacuoles are relatively small, typically ranging from 50 to 500 nanometers in size. In contrast, plant cells contain a large central vacuole that can occupy between 30% and 90% of the cell's total volume, depending on the cell type and developmental stage. They act as storage compartments that can hold a variety of substances, including water, ions, nutrients, waste products, and pigments.

Vacuoles are essential for various cellular functions. They store water, nutrients, and waste products. Their ability to regulate water content helps maintain cell shape and rigidity, contributing to turgor pressure, the internal pressure exerted by

* **Corresponding author K.N. Aruljothi:** Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India; E-mail: aruljotn@srmist.edu.in

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the vacuole in/within the cell. Additionally, vacuoles are crucial for maintaining the pH of the cell's internal environment through proton pumps and ion exchange, ensuring optimal conditions for cellular processes like enzyme activity and metabolism. They also serve as detoxification centers, storing harmful substances. Furthermore, vacuoles are responsible for pigmentation by storing pigments like anthocyanins and carotenoids that provide color to flowers, fruits, and leaves. Lastly, they play a role in autophagy, a cellular process that involves breaking down cellular components.

The discovery of vacuoles dates back to the early days of microscopy. While Anton van Leeuwenhoek is often credited in the late 17th century for his observations of single-celled organisms, earlier scientists likely observed vacuoles using basic microscopes. As microscopy techniques advanced, scientists began to appreciate the diversity and significance of vacuoles in different cell types. While the term “vacuole” comes from the Latin word “vacuoles,” which means “empty,” the organelle is not truly empty space but instead contains a variety of substances. Research on vacuoles remains a vital area in cell biology, with scientists investigating their roles in plant growth, development, and responses to stress.

Types of Vacuoles

Plant Vacuoles

In plant cells, the central vacuole is the most prominent type of vacuole. This large, membrane-bound organelle takes up a significant portion of the cell's volume. The central vacuole is surrounded by a membrane called tonoplast, which is also known as the vacuolar membrane. The central vacuole serves various functions, including:

- Storage: It stores water, nutrients, ions, toxins, and waste products.
- Turgor pressure: The pressure exerted by the fluid inside the vacuole maintains the cell's rigidity and the cell’s structure.
- pH regulation: It regulates the pH of the cell's internal environment.
- Detoxification: It stores harmful substances.
- Pigmentation: It contains pigments that provide colour to flowers, fruits, and leaves.
- Autophagy: It breaks down cellular components.

There are primarily two types of plant vacuoles.

- Lytic Vacuole (LV): LVs are developed early during embryogenesis. These vacuoles help in breaking down unwanted cellular substances using hydrolase

enzyme. Therefore, hydrolase enzyme are very crucial in the degradation and recycling of cellular substances [1].

- Protein Storage Vacuole (PSV): PSVs are formed after LVs during embryogenesis. In addition, in maturing seeds, LVs are transformed to PSVs, but during germination, this process is reversed. These vacuoles are used to store nutrients and proteins, which may be needed at different stages of growth or under stress conditions. It's possible for protein storage vacuoles and lytic vacuoles to combine to form a large central vacuole [1].

Animal Vacuoles

Animal cells typically lack the large, central vacuoles that are characteristic of plant cells. Nevertheless, they possess various smaller vacuoles that fulfill specific roles. These vacuoles are generally less prominent than the central vacuoles found in plants.

Different Types of Vacuoles Present in Animals

Food Vacuoles - These are membrane-bound structures that form when cells take in food particles through a process called phagocytosis. They merge with lysosomes, which contain enzymes for digestion, to break down the ingested food.

Autophagic Vacuoles - These are created when cells need to recycle their own materials. They engulf damaged organelles or cellular waste and transport them to lysosomes for breakdown.

Secretory Vacuoles - These vacuoles are responsible for storing and releasing substances like hormones or neurotransmitters.

Contractile Vacuoles - Although more commonly found in protists, these vacuoles can sometimes be present in animal cells, particularly those in hypotonic environments. They play a role in osmoregulation by maintaining the cell's water balance and expelling excess water.

Fungal Vacuoles

Fungal vacuoles are organelles that carry out a variety of essential functions for the growth, differentiation, symbiosis, and pathogenesis of fungi. These acidic storage compartments are involved in protein degradation, maintaining cellular homeostasis, membrane trafficking, signalling processes, and nutrient storage. They play a role in glycoprotein turnover and hydrolysis, store phosphate, calcium, and amino acids, and help regulate pH, ion homeostasis, osmotic balance, and cytoplasmic detoxification. Additionally, they are crucial for

CHAPTER 9

Plasma Membrane: Gateway and Sentinel of Cellular Exchange

S. Aswini[1], K. Kumaran[1], Sanjana Dhayalan[1], Prakash Gangadaran[2,3,4,*] and **K.N. Aruljothi[1]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

[2] *Department of Nuclear Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea*

[3] *Cardiovascular Research Institute, Kyungpook National University, Daegu, Republic of Korea*

[4] *BK21 FOUR KNU Convergence Educational Program of Biomedical Sciences for Creative Future Talents, School of Medicine, Kyungpook National University, Daegu, Republic of Korea*

Abstract: The plasma membrane is a critical cellular structure that acts as a selective barrier, controlling the movement of molecules in and out of the cell while enabling communication with the external environment. This chapter provides an in-depth exploration of the plasma membrane, beginning with its structure and the fluid-mosaic model, which describes the dynamic organization of lipids, proteins, and carbohydrates. It then examines the various functions of the membrane, including maintaining cellular integrity, supporting signal transduction, and regulating the movement of substances through mechanisms like passive diffusion, facilitated diffusion, active transport, and group translocation. Key transport proteins such as glucose transporters and ion channels are discussed in detail, highlighting their roles in maintaining cellular homeostasis. The chapter also addresses the pathological significance of plasma membrane dysfunction, linking abnormalities to diseases such as hypertension, sphingolipid-related disorders, and neuronal vulnerabilities. Further, it explores the role of the plasma membrane in neurotrophic signaling and insulin regulation. Finally, recent advances in therapeutic approaches, including CAR-T cell therapy and liposomal drug delivery systems, are examined for their potential in disease treatment.

Keywords: Active Transport, Aquaporin, Bilayer, Diffusion, Endocytosis, Exocytosis, Facilitated Diffusion, Insulin, Lipid Raft, Membrane Potential, Neurotransmitter, Phospholipid, Potassium Channel, Sphingolipidoses..

[*] **Corresponding author Prakash Gangadaran:** Department of Nuclear Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea; E-mail: prakashg@knu.ac.kr

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INTRODUCTION

The plasma membrane is a lipid bilayer with embedded proteins that control the movement of substances in and out of the cell while enabling interactions. Organellar membranes have a similar structure but differ in composition and function based on the organelle's role. Membrane-bound organelles include the mitochondria, endoplasmic reticulum, Golgi apparatus, lysosomes, and peroxisomes. Non-membranous organelles include ribosomes, centrioles, cilia, and flagella [1].

STRUCTURE

Gorter and Grendel Membrane Theory (1920)

This theory proposes that the plasma membrane is made up of a lipid bilayer. An experimental investigation on erythrocytes from different sources was carried out, and the experimental results supported their hypothesis. Gorter and Grendel failed to explain the membrane functions and could not explain the other membrane components other than lipids. This model set the stage for later models by highlighting the importance of lipid organization (Fig. **1**) [2].

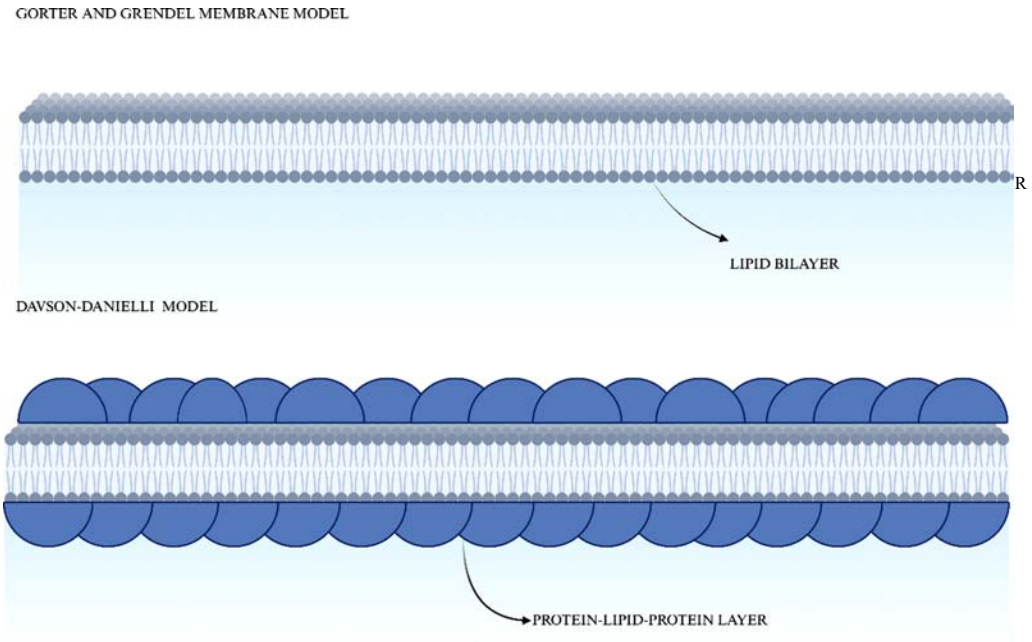

Fig. (1). Depiction of the difference between the garter and Grendel membrane model and the Davson-Danielli model.

Pauci-molecular Theory

In 1935, Davson and Danielli came up with a model for plasma membrane called the Pauci-molecular theory. According to this theory, the membranes have a central “lipoid” region, which in general is surrounded by monolayers of lipids and is covered by protein sheets. This model is like a sandwich model made of protein-lipid-protein. In the year 1959, J. David Robertson proposed that all the cellular membranes possess a similar underlying structure, the unit membrane. He used extensive metal staining for the visibility of plasma membranes under an electron microscope. When observed under a microscope, the cell membrane exhibits a trilaminar appearance, featuring a lighter inner region and two darker outer regions. Robertson noted that the membrane consists of a lipid bilayer with sheets of mucoproteins on both sides, which supports the pauci-molecular theory [3]. The pauci-molecular theory proposed that all the membranes have equivalent structure, the same thickness, and the same lipid-protein ratio in the membrane surface. The Pauci-molecular theory couldn't explain the presence of membrane proteins outside the membrane or the active transport of macromolecules. It also failed to account for the dynamic nature and heterogeneity of membrane structures. Until 1972, the most accepted plasma membrane model was the pauci-molecular theory. After 1972, the scenario completely changed [4].

Fluid Mosaic Model (1972)

S. Jonathan Singer and Garth Nicolson proposed the fluid-mosaic model. This theory says that the plasma membrane is made up of a lipid bilayer where proteins are embedded in it. The phospholipid bilayer illustrates the effects of hydrophilic and hydrophobic interactions in lipids. The non-polar fatty acid chains of the phospholipid stand away from being in contact with water by increasing the hydrophobic interaction. The ionic groups are in direct contact with the aqueous phase, thereby giving rise to hydrophilic interactions. The hydrophilic and hydrophobic interactions are crucial for maintaining the membrane's integrity and functionality, as they help create a stable barrier that controls the movement of substances in and out of the cell. The dipole-dipole interaction between ionic pairs of phosphatidylcholines (zwitterionic phospholipid) is the reason for the stable lipid bilayer structure. According to this theory, there are two types of membrane proteins-peripheral and integral (Fig. **2**).

CHAPTER 10

Mitochondria and Chloroplasts: Evolutionary Engines of the Cell

K. Kumaran[1,†], Keerthana Ramesh[1,†], Sanjana Dhayalan[1], Gargii Chatterjee[1] and **K.N. Aruljothi[1,*]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

Abstract: Mitochondria and chloroplasts are essential organelles driving energy production and metabolism in eukaryotic cells. Mitochondria, known as the cell's "powerhouses," generate ATP through oxidative phosphorylation, utilizing nutrients to fuel cellular processes. According to the endosymbiotic theory, mitochondria originated from free-living bacteria, and their distinct mitochondrial DNA (mtDNA) is maternally inherited. Dysfunction in mitochondria—often due to accumulation of mtDNA mutations—is associated with neurodegenerative diseases, metabolic syndromes, and cancer, with recent studies revealing their roles in aging and disease. These insights are advancing therapies to improve mitochondrial health, and genome editing now holds the potential for correcting pathogenic mtDNA mutations. Chloroplasts in plant cells are essential for photosynthesis, synthesizing carbohydrates, amino acids, fatty acids, and membrane lipids. Chloroplasts are sensitive to temperature stress, and their malfunction can produce Reactive Oxygen Species (ROS), which may be fatal to plant cells. This sensitivity makes chloroplast health crucial for plant resilience, especially under climate stress. Future research in mitochondrial and chloroplast should concentrate on offering potential treatments for human diseases and developing stress-resistant crops. Genome editing technologies could address mitochondrial and chloroplast dysfunction, creating innovative therapies and sustainable agricultural practices to address health and environmental challenges.

Keywords: Cellular Respiration, Endosymbiotic Theory, Energy Production, Electron Transport Chain, Krebs Cycle, Mitochondria-Associated Membranes (MAMs), Mitochondrial DNA (mtDNA), Oxidative Phosphorylation, Reactive Oxygen Species (ROS), Uniparental Inheritance..

[*] **Corresponding author K.N. Aruljothi:** Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India; E-mail: aruljotn@srmist.edu.in

[†] Equal contribution.

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MITOCHONDRIA

Introduction

It was close to a billion years since cellular respiration had become a vital part of the cell when science discovered the pan portion of the cell during the middle of the nineteenth century. Based on light microscopy, the first diagrams of cellular structure showed the existence of granular structures known as mitochondria in the cell's cytoplasm. The first observation of the presence of mitochondria in muscle cells was made during the 1850s by the anatomist Kölliker (1856). However, in the 1890s, Altman devised a fantastic proposal: the granules, which Deichmann called "bioclasts," were symbiotes. This idea was expanded on by Mereschkowsky in 1905.

The same idea concerning chloroplasts was first proposed by C. Simons in 1883, before Schimper. The term "Mitochondrion" was first used to explain data by Benda in 1898. The name is derived from the Greek terms: "mitos" in thread, referring to an activity in the mitotic field, and "chondros" in grain, referring to an activity associated with spermatogenesis. As mitochondria are the primary site of energy conversion in the cell, or where "cellular respiration" takes place, they are also known as the organelles that produce blood inside the cell. However, the causes of such a phenomenon were not studied until the 1950s, before the genesis of mitochondria was considered. Very early in the 1950s, Mitchell (1952) and Ephrussi (1950) reported post-Mendelian genetic variation to control the forces determining the division of yeast mitochondria. A little while later, McLean *et al*. (1958) reported that mitochondria can synthesize polypeptides. Luck and Reich 1964), Nass, early in the nineteen sixties, since many groups. Their significant contributions regarding the mitochondria and their invention of the mitochondrion were related. However, the hypothesis on the endosymbiotic origin of mitochondria, which had existed, started to attract new and enthusiastic followers in the 1960s with the introduction of new biochemical methods. It would be superfluous to emphasize that the discovery of the DNA contained within the organelles and the non-classical inheritance of organelles were the two components that contributed to the resurgence of interest.

Once Margulis had rephrased the endosymbiotic theory into endosymbiosis (1970), it became recognized how mitochondria have evolved into the cell. It is accepted that the mitochondrion originated from a free-living bacterium. However, there is still an argument regarding how this endosymbiosis came about and which living things this process encompassed. There are about a hundred years between the first reports of mitochondria and the modern understanding of the structure, function, inheritance, and origin of mitochondria. Since 2003, the

work of Tsang and Lemire has made it possible to identify the mitochondrial genomes of more than 250 species by examining the effects of mutations in several mitochondrial genes.

Origin and Evolution of Mitochondria

Mitochondria in eukaryotes are suspected of having an endosymbiotic origin. In the 1960s, Margulis Marshaled confirmed this hypothesis based on two factors, *i.e*., the presence of DNA and a separate translational system distinct from one in the cytosol. Further elaborate studies of mitochondrial genomes and genes proclaim that mitochondria have a bacterial origin. However, another theory explained the mitochondrial origin, *i.e*., the hydrogen hypothesis given by Martin and Muller in 1998. According to this, the origin of heterotrophic organelles and other eukaryotes was identical.

The symbiotic origin is based on two subjects: the "Archezoan Scenario" and the "Symbiogenesis Scenario." The former is based on endosymbiosis and the latter on the hydrogen hypothesis. The archean scenario explains the presence of a proto-mitochondrial endosymbiont in mitochondrial eukaryotes, and the symbiogenesis scenario explains the hold of an alpha proteobacterium in an archaebacterial cell [1, 2].

Mitochondrial Inheritance in Eukaryotes

The mitochondrion is usually inherited from a single parent (maternal inheritance). This is responsible for the offspring's homoplasmy (where all mtDNA are genetically identical)—the disruption of MT homoplasmy results in mitochondrial dysfunction and cancer in human beings. There are two methods for ensuring mtDNA homoplasmy: (i) Strict Maternal Inheritance (SMI) and (ii) the bottleneck mechanism. A strict maternal inheritance pattern is observed in the shell coiling of snails (*Limnaea stagnalis*). The three stages that control the bottleneck mechanism are:

(i) A bottleneck that occurs during oogenesis expresses mutations that allow purification before the resumption of replication during the oocyte's maturity, lowering the copy number of mtgenes.

(ii) Selective replication during oogenesis led to the establishment of a genetic bottleneck.

(iii) Another one forms during embryogenesis.

Recent reviews provide a glimpse into the status of maternal inheritance research (reviews are available in Jokinen and Battersby 2013 and Mishra and Chan 2014).

CHAPTER 11

Cytoskeleton: The Cell's Backbone and Highway

Danyal Reyaz[1], Sparshika Mishra[1], Ranjini Sengupta[1], T. Sasitharan[1], S. Gnanavel[2] and **K.N. Aruljothi[1,*]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

[2] *Department of Biomedical Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

Abstract: The cytoskeleton is an essential framework in eukaryotic cells, providing structural support, maintaining shape, and facilitating intracellular transport and movement. This chapter explores the key components of the cytoskeleton: microfilaments, intermediate filaments, and microtubules, discussing their structures, assembly mechanisms, and roles in cellular processes. Microfilaments, composed of actin, contribute to cellular shape, movement, and muscle contraction through mechanisms like treadmilling and interaction with myosin. Intermediate filaments, including keratin and vimentin, provide mechanical strength and support cellular integrity under stress. Microtubules, composed of tubulin, are involved in mitosis, intracellular transport, and the maintenance of cell polarity. Additionally, this chapter delves into the role of motor proteins like kinesin and dynein in facilitating molecular transport along microtubules and how cytoskeletal dynamics are crucial for both healthy cellular function and pathological conditions like cancer and neurodegenerative diseases.

Keywords: Actin, Cancer, Cell Motility, Dynein, Intermediate filaments, Keratin, Kinesin, Locomotion, Microfilaments, Microtubules, Muscle, Neurodegenerative Diseases.

INTRODUCTION

In addition to the cytoplasm, plasma membrane, and organelles, eukaryotic cells have something like a hidden superhero called the cytoskeleton. This internal framework comprises tiny fiber proteins, which we call cytoskeletal fibers. The cytoskeletal fibers play a critical role in maintaining cellular integrity by preserving cell shape and providing mechanical support. The plasma membrane functions as a selective barrier that protects the intracellular environment. Within

* **Corresponding author K.N. Aruljothi:** Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India; E-mail: aruljotn@srmist.edu.in

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the cytoplasm, distinct organelles carry out specialized biochemical processes: mitochondria facilitate ATP production through cellular respiration, the Golgi apparatus is responsible for protein modification and trafficking, and the endoplasmic reticulum is involved in protein synthesis and intracellular storage. Now, let us talk about the cytoskeleton. Think of it as the house's skeleton. Just like our bones give our bodies structure, these cytoskeletal fibers give the cell its shape and help it stay strong. They're like the support beams in our house. But the cytoskeleton does more than that. It's like the cell's personal trainer. It helps the cell move around, divide into two when it needs to make a copy of itself, and even helps things move around inside the cell. So, in simple terms, the cytoskeleton is like the cell's own hero, working behind the scenes to keep everything in order, maintain shape, and ensure the cell can do everything it needs to do [1].

Types of Cytoskeletal Fibers

The cytoskeleton is a complex network of fibers that provides structural support, shape, and organization to cells. It plays a critical role in various cellular processes, including movement, division, and intracellular transport. This dynamic system is made up of different types of protein-based filaments, each contributing to specific cellular functions (Table **1**).

Table 1. Types of protein present in the cytoskeleton, along with the protein size.

Type	Protein	Site	Size (kDa)
I	Acidic Keratins	Epithelial Cells	40-60
II	Neutral or Basic Keratins	Epithelial cells	50-70
III	Vimentin Desmin Glial fibrillary acidic proteins Peripherin	Fibroblasts, white blood cells, and other cell types Muscle cells Glial cells Peripheral neurons	54 53 51 51
IV	Neurofilament proteins NF-L NF-M NF-H α-Nexin Nestin	 Neurons Stem cells	 67 150 200 66 200
V	Nuclear lamins	Nuclear lamina of all cell types	60-75

The three types are:

- Microfilaments
- Intermediate filaments
- Microtubules

MICROFILAMENTS

Structures that were a part of the cytoskeleton that supported the flexibility and increased the strength of the cell were found in 1974 by B. Paleviz *et al*. They are microfilaments, as we now refer to them.

Structure

Microfilaments are little rod-shaped structures approximately 6 nm in diameter, found inside the cytoskeleton of eukaryotic cells. Microfilaments are constituted by the aggregation of actin monomers. It comprises two strands of actin protein subunits coiled in a helical formation, hence referred to as actin filaments. The actin subunits that constitute microfilaments are globular actin (G-actin), which, upon polymerization, are referred to as filamentous actin (F-actin). The actin subunits assemble directionally to produce microfilaments. Subunits possess a "top" and a "bottom," with the top of one subunit consistently interacting with the bottom of another. The terminal subunit of a filament is referred to as the negative (-) end, while the opposing end, which experiences greater polymerization, is designated as the plus (+) end. Microfilaments possess polarity, although this pertains solely to their directionality and is unrelated to electrical charge [2] (Fig. **1**).

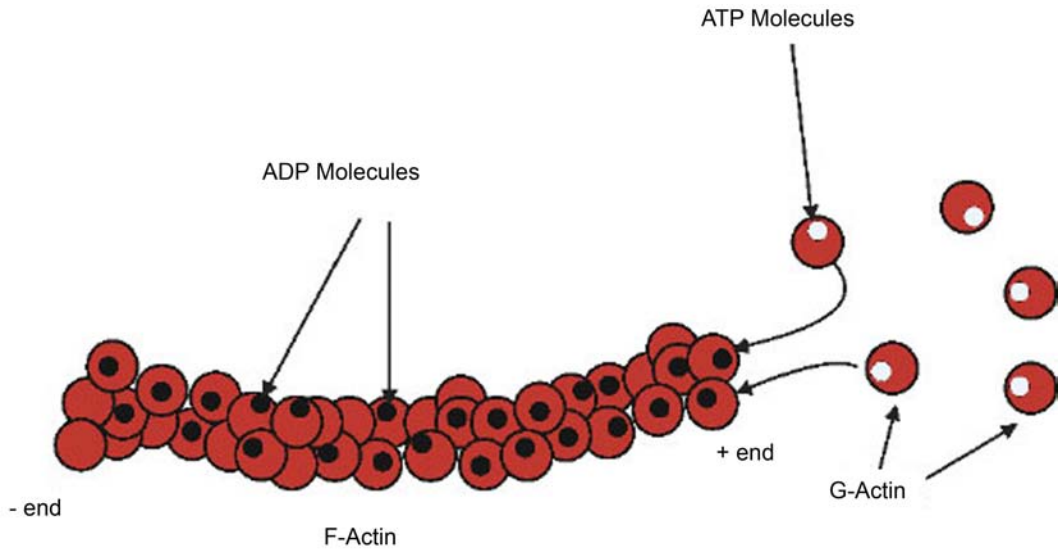

Fig. (1). Structure and assembly of microfilaments.

CHAPTER 12

Signal Transduction Pathways Orchestrate Cellular Communication: A Narrative Review

Kruthika Prakash[1], Raksa Arun[1], Srisri Satishkartik[1], Sayantani Chattopadhyay[1], Mashira Rahman[1], Prakash Gangadaran[2,3,4,*] and **K.N. Aruljothi[1]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

[2] *Department of Nuclear Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea*

[3] *Cardiovascular Research Institute, Kyungpook National University, Daegu, Republic of Korea*

[4] *BK21 FOUR KNU Convergence Educational Program of Biomedical Sciences for Creative Future Talents, School of Medicine, Kyungpook National University, Daegu, Republic of Korea*

Abstract: Cell signaling and signal transduction coordinate cellular communication and the execution of diverse biological functions. This review synthesizes how cells sense and integrate external and internal cues through core pathways, with emphasis on G Protein–Coupled Receptor (GPCR) and Mitogen-Activated Protein Kinase (MAPK) cascades that govern growth, differentiation, and apoptosis. We outline the roles of second messengers, protein kinases, and transcription factors in propagating and tuning signals, and describe regulatory mechanisms that maintain fidelity and specificity. We also summarize how pathway dysregulation underlies disease, including cancer, and discuss the therapeutic implications of targeting signaling networks.

Keywords: Cell signaling, Signal transduction, GPCR, MAPK, Second messengers, Protein kinases, Transcription factors, Apoptosis.

INTRODUCTION

Cell signaling enables cells to communicate with each other and with their environment to sustain physiological function. This communication network is essential for organismal growth, adaptation, and survival in dynamic contexts [1]. Signal transduction converts extracellular and intracellular cues into specific

* **Corresponding author Prakash Gangadaran:** Department of Nuclear Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea; E-mail: prakashg@knu.ac.kr

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cellular responses, ensuring appropriate reactions to stimuli associated with immune defense, growth, differentiation, and other core processes [2].

Signals include hormones, growth factors, neurotransmitters, and environmental inputs such as temperature and light [3]. Cells operate within integrated networks that support organismal health. Cell signaling coordinates growth and development, maintains homeostasis, mediates immune responses, and ensures proper nervous system function [4].

Multicellular organisms develop from a single fertilized egg through cell division, differentiation, and controlled tissue formation, all tightly regulated by signaling pathways [5]. During embryogenesis, signaling molecules guide cell positioning and organogenesis by activating gene programs for specialization [6]. To preserve a stable internal environment, cells continuously sense changes in temperature, nutrient levels, and pH and adjust their activity to restore equilibrium [7]. Hormones such as insulin and glucagon exemplify signaling molecules that regulate metabolism and energy balance [8].

The immune system relies on signaling to detect and eliminate pathogens. Immune cells such as T cells and B cells use signaling to recognize invaders, activate other immune cells, and coordinate an effective defense through cell–cell communication [9]. Neurons communicate *via* electrical and chemical signals to transmit information across extensive networks; neurotransmitters enable rapid, coordinated responses underlying movement, sensation, and cognition [10].

TYPES OF CELL SIGNALING

Cell signaling employs distinct modes of communication defined by distance and delivery. The four principal forms are autocrine, paracrine, endocrine, and juxtacrine signaling.

Autocrine Signaling

In autocrine signaling, a cell releases signaling molecules that bind receptors on its own surface. This feedback modulates the cell's activity and is especially important in development and immune responses [11]. Cancer cells often exploit autocrine loops to drive their growth and survival.

Paracrine Signaling

In paracrine signaling, cells secrete molecules that act on nearby cells, mediating local communication [12]. During tissue development and repair, growth factors stimulate adjacent cells to proliferate and divide; paracrine cues similarly coordinate wound healing [13].

Endocrine Signaling

Endocrine signaling involves hormone release into the bloodstream, allowing signals to reach distant targets. This long-range communication coordinates metabolism, development, and reproduction across organ systems; endocrine glands such as the pituitary, thyroid, and pancreas orchestrate these responses [14].

Juxtacrine Signaling

In juxtacrine signaling, cells communicate through direct physical contact. Membrane-bound ligands on one cell engage receptors on an adjacent cell, triggering local responses. During embryonic development and tissue differentiation, where precise cell-to-cell interactions build ordered structures, juxtacrine signaling is essential [15].

Role of Signal Transduction in Cellular Communication

After a signal reaches its target cell, it must be converted into a specific intracellular response—a process termed signal transduction. Signal transduction comprises sequential molecular events that amplify and relay information from the cell surface to the intracellular machinery that produces the appropriate response. Major components include:

Receptors

Receptors reside on the cell surface or within the cell and bind specific signaling molecules; they are the first points of contact for external cues [16]. Two principal classes of cell-surface receptors mediate signal transduction: G Protein-Coupled Receptors (GPCRs) and Receptor Tyrosine Kinases (RTKs) [17]. Ligand binding induces a conformational change that initiates the intracellular signaling cascade [18].

Signaling Molecules

Signaling molecules—such as hormones, growth factors, and neurotransmitters—are released by a cell and bind receptors on target cells to initiate transduction [19]. Insulin, for example, binds its receptor to regulate glucose uptake and metabolism [20].

Signal Transduction Proteins

Once receptors are activated, intracellular signaling proteins propagate and amplify the signal, often through cascades in which one protein activates the next

CHAPTER 13

Cell Death: Mechanisms and Mysteries beyond Apoptosis

Shambhavi Jha[1], Rohan Vyas[1], S. Manvi[1], Vasanth Kanth T.L.[1], Keerthivasu Ramasamy[1], K.N. Aruljothi[1] and **Ramya Lakshmi Rajendran[2,3,4,*]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

[2] *Department of Nuclear Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea*

[3] *Cardiovascular Research Institute, Kyungpook National University, Daegu, Republic of Korea*

[4] *BK21 FOUR KNU Convergence Educational Program of Biomedical Sciences for Creative Future Talents, School of Medicine, Kyungpook National University, Daegu, Republic of Korea*

Abstract: This book chapter on cell death explores the mechanisms, significance, and implications of various forms of cellular demise in health and disease. It delves into classic pathways like apoptosis, which ensures cellular homeostasis, immunity, and necrosis, traditionally viewed as accidental cell death but now recognized for its role in inflammation and tissue damage. Emerging forms of cell death, such as autophagy, pyroptosis, ferroptosis, and NETosis, highlight the complexity of cellular life and death decisions. The chapter underscores how each form of death is tightly regulated by specific signaling pathways and proteins, contributing to tissue development, immune responses, and the progression of diseases like cancer and neurodegenerative disorders. A particular focus is placed on the molecular crosstalk between these pathways and their potential as therapeutic targets. The historical context of cell death research—from identifying apoptosis to modern-day advancements in targeted therapies and gene-editing technologies—provides a comprehensive view of how our understanding of cellular death has evolved.

Keywords: Apoptosis, Autophagy, Cancer, Disorders, Ferroptosis, Immune responses, Necrosis, NETosis, Neurodegenerative, Pyroptosis, Signalling pathways, Therapeutic targets.

* **Corresponding author Ramya Lakshmi Rajendran:** Department of Nuclear Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea; E-mail: ramyag@knu.ac.kr

K.N. Aruljothi, Prakash Gangadaran, Krishnan Anand, Satish Ramalingam, K. Kumaran & Kruthika Prakash (Ed.)

INTRODUCTION

In the intricate tapestry of life, cell death stands as a cornerstone, shaping the very essence of biological existence. It is a process as ancient as life itself, a fundamental mechanism intricately woven into the fabric of development, homeostasis, and disease. Cell death is not a mere cessation of cellular activity; instead, it is a meticulously regulated, multifaceted series of events that culminate in the demise of a living entity. Beyond its apparent simplicity lies a world of complexity, where cellular components intricately communicate and orchestrate a symphony of self-destruction. The study of cell death has transcended the realms of mere biological inquiry; it has become a frontier where life sciences, genetics, and medicine converge. At its core, cell death represents nature's ultimate balancing act. It is the balance of nature, which calls for everything that is ever born to meet its end, its death. Every human, every microbe has a certain life span, after which death is inevitable. This concept, at the most cellular level, is more frequent and much more complex. There are countless cells in our body dying every day, and countless still that are newly generated. It is a process of profound importance, eliminating cells that have outlived their usefulness, have suffered irreparable damage, or have succumbed to genetic aberrations. This process is indispensable in sculpting and developing organisms and ensuring the proper formation of tissues, organs, and intricate structures [1]. Additionally, cell death acts as a guardian, protecting the organism from potential threats. It is the body's natural response to infections, injuries, and internal dysregulation that underlie various diseases, preventing the spread of damage to neighbouring cells and tissues. Yet, the significance of cell death extends far beyond its role as a biological safeguard. It is a process deeply entwined with the very essence of evolution. The ability to control cell death has played a pivotal role in the emergence of complex life forms, allowing for the development of intricate biological systems. In essence, the study of cell death is a study of life itself—a journey into the heart of existence, exploring the delicate balance between creation and destruction, growth and decay [2, 3].

In this chapter, we embark on a comprehensive exploration of cell death. We delve into the mechanisms that govern this intricate process, uncovering the molecular intricacies that define its various forms. From the classic pathways of apoptosis and necrosis to the emerging realms of autophagy, pyroptosis, and ferroptosis, we unravel the mysteries that underlie each type of cellular demise. Moreover, we examine the physiological significance of cell death, its pivotal role in development, tissue maintenance, and immunity, as well as its implications in diseases ranging from cancer to neurodegenerative disorders. As we venture deeper into the labyrinth of cell death, we also cast our gaze towards the future. Recent advancements in the field have opened new avenues of research,

promising innovative therapies and treatments. From targeted therapies tailored to specific cell death pathways to the revolutionary potentials of gene-editing technologies, the landscape of cell death research is constantly evolving [4].

The Historical Tapestry of Cell Death Research

The annals of cell death research are rich with the endeavours of pioneering scientists whose meticulous observations and ingenious experiments have illuminated the enigmatic pathways of cellular demise. Our journey through time takes us back to the 19th century, when rudimentary microscopes provided the first glimpses into the microscopic world. Eminent scientists like Rudolf Virchow and Carl Vogt observed cellular structures and noted instances where cells seemed to disintegrate, laying the foundation for the intriguing field of cell death studies. In the early 20th century, the term “apoptosis” made its debut in scientific discourse, thanks to the work of Walther Flemming. This term, embodying the Greek notion of a “falling off” or “dropping,” encapsulated the elegant yet complex process of programmed cell death. Flemming's observations sparked curiosity, fuelling a wave of research that sought to unravel the mysteries of apoptosis [1]. Amidst these explorations, the mid-20th century heralded significant breakthroughs. Pioneering electron microscopy techniques provided unprecedented resolution, enabling scientists to delve deeper into cellular structures and observe the orchestrated disassembly of dying cells. It was during this period that the morphological hallmarks of apoptosis—cell shrinkage, membrane blebbing, chromatin condensation, and formation of apoptotic bodies—were meticulously documented, offering a profound understanding of this fundamental process (Table **1**) [5].

In the latter half of the 20th century, the scientific community witnessed the emergence of groundbreaking discoveries. A key milestone came in the form of the identification of caspases, the enzymatic executioners orchestrating apoptosis. The elucidation of these proteases' role in cleaving vital cellular substrates offered a molecular perspective, transforming apoptosis from a mere morphological phenomenon into a finely regulated biochemical cascade. As the 21st century dawned, the exploration of cell death expanded beyond apoptosis. Necrosis, once deemed a chaotic and uncontrolled form of cell death, was redefined. It became evident that necrosis, too, had regulatory elements, especially in the context of ischemic injury and inflammation. Concurrently, autophagy, a cellular recycling mechanism, garnered increasing attention. Its role in maintaining cellular homeostasis, particularly during periods of stress and starvation, unfolded as researchers decoded the intricate machinery of autophagosome formation and cargo recognition. The modern era of cell death research is marked by a profound transformation catalysed by advances in molecular biology, genetics, and high-

CHAPTER 14

Stem Cells: Breakthroughs in Medicine and Therapeutics

Vanshikaa Karthikeyan[1], Janani Balaji[1], SriSri SatishKartik[1], Dannie Macrin[2,*] and **K.N. Aruljothi[1]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

[2] *Department of Computational Biology, Institute of Bioinformatics, Saveetha School of Engineering, SIMATS Saveetha Institute of Medical and Technical Sciences, Chennai, India*

Abstract: Stem cells are usually referred to as undifferentiated cell masses, which can differentiate into many cell types. Stem cells are present in all organisms in various evolved forms. These cells can self-renew. Additionally, stem cells can be broadly classified based on their origin and differentiation potential. Thus, the therapeutic potential of these cells can be harnessed and utilized to treat various disorders, including blood disorders, tissue and organ regeneration, and others, which can be classified under the division of stem cell therapy. Although stem cells possess the capacity for use in disease treatment, their implementation also has its own risks. This chapter covers the basics of stem cells, including the associated cell types, applications, epigenetics, and recent trends.

Keywords: Blood disorders, Differentiation potential, Epigenetics, Recent trends, Stem cell therapy, Stem cells, Tissue regeneration.

INTRODUCTION

Stem cells are defined as undifferentiated masses of cells present in all living organisms. Furthermore, stem cells represent the building blocks of all tissues and organs, with major properties including:

i. Extensive proliferation
ii. An ability to arise from a single cell (clonal).
iii. An ability to differentiate to form different cell types (potency).

* **Corresponding author Dannie Macrin:** Department of Computational Biology, Institute of Bioinformatics, Saveetha School of Engineering, SIMATS Saveetha Institute of Medical and Technical Sciences, Chennai, India; E-mail: danniem.sse@saveetha.com

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However, these properties vary among the different cell types. For instance, Embryonic Stem Cells (ESCs) undergo extensive proliferation, whereas Adult Stem Cells (ASCs) primarily differentiate into tissue-specific cells.

Thus, stem cells are currently employed in cell therapy and drug development processes. Additionally, stem cells have improved understanding of pathogenesis. Nonetheless, despite these significant advances in stem cell biology, certain ethical issues remain that limit the utilization of these cells [1].

STEM CELL FUNCTIONS

Stem cells are predominantly used due to their ability to self-renew and differentiate into various types of cells. In adult organisms, stem cells can either actively replenish tissues to repair damage or remain dormant, as is the case with neural stem cells in the mammalian brain. There are two types of stem cell division: Symmetric and asymmetric. Symmetric division occurs when the cells reproduce to produce more identical cells, while asymmetric division occurs when the cell differentiates to form a specific cell type. In the asymmetric model, the stem cell forms an exact copy and one differentiated cell, which helps maintain the homeostasis of the stem cell pool at the individual level. A major disadvantage of asymmetric division is that the stem cell pool cannot be replenished at the time of injury. However, this limitation can be resolved by the symmetric division, which maintains the homeostasis of the stem cell pool at the population level. Meanwhile, two types of symmetric division exist: the first is a proliferation division, which leads to the formation of two stem cells; the second is a differentiation division, which leads to the formation of two differentiated cells. Proliferation and differentiation of these cells occur due to the signals from the surrounding tissues as well as the stem cell [2, 3].

TYPES OF STEM CELLS

Stem cells are classified based on the following factors:

i. Differentiation potential
ii. Origin

Stem Cells Based on Differentiation Potential

The ability of stem cells to differentiate is based on their origin and associated derivation; thus, stem cells can be divided into five major categories.

Totipotent/Omnipotent Stem Cells

These are the cells that have the potential to differentiate into the various cell types found in the entire organism. Totipotent cells have the highest potential to differentiate. For example, the zygote is a totipotent cell that can differentiate into all cell types, including the three germ layers and extraembryonic tissues, such as the placenta. Meanwhile, totipotent cells found in an embryo differentiate into the inner cell mass (ICM) and the extra-embryonic cell lineage, such as the trophectoderm. These totipotent embryos exhibit a unique transcriptome, characterized by dramatic changes in epigenetic and chromatin features, including the de novo assembly of nucleosomes, demethylation of DNA, chromatin remodeling, and histone modifications.

Pluripotent Stem Cells

These stem cells play a crucial role in forming the three primary germ layers, which, in turn, help develop all tissues and organs: ectoderm, mesoderm, and endoderm. These stem cells are only short-lived during the early stages of embryo development; however, pluripotent stem cells can develop into either fetal cells or adult cells, but not into a complete organism. However, these cell lines can be immortalized and grown *in vitro*. These cells can then differentiate into all cell types through various mechanisms, similar to those employed by ESCs.

Multipotent Stem Cells

Meanwhile, Multipotent Stem Cells (MSCs) have a more restricted differentiation potential, transitioning to specific cell types within a particular lineage. For example, Hematopoietic Stem Cells (HSCs) can differentiate into different types of blood cells. These cells are considered ASCs due to their limited capacity for differentiation and multipotency. MSCs are found in various organs, including the periosteum, adipose tissue, placenta, dermis, and umbilical cord blood. MSCs can be identified by their adherence and the ability to differentiate into cartilage, fat, and bone, as well as the expression of markers, such as CD90, CD105, and CD73. Currently, these cells are being used in tissue healing, development, and defense.

Oligopotent Stem Cells

These cells possess the ability for self-renewal and can differentiate into various types of cells. Moreover, these stem cells can be viewed as progenitor cells for ASCs and can differentiate into specific cell types; for example, myeloid stem cells can differentiate into white blood cells but not red blood cells. Furthermore, these progenitor-oligo cells have also been observed to differentiate into more mature cells, such as alveolar epithelial cells and bronchiolar epithelium.

CHAPTER 15

Cancer Stem Cells: Catalysts of Cancer Progression

Vedika Kartha[1], Saloni Semwal[1], Lakshmi Sai Varshini Yedavalli[1], Disha Kamath[1], S. Pooja[1], Dannie Macrin[2], Satish Ramalingam[1,*] and **K.N. Aruljothi[1]**

[1] *Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India*

[2] *Department of Computational Biology, Institute of Bioinformatics, Saveetha School of Engineering, SIMATS Saveetha Institute of Medical and Technical Sciences, Chennai, India*

Abstract: Within tumors, a small number of cells exist alongside the majority of more rapidly dividing cells that constitute most of the tumor. This slowly growing subset of cells is referred to as cancer stem cells (CSCs), and they can regenerate themselves, allowing for the continuous growth of the tumor. CSCs were first reported in acute myeloid leukemia by Bonnet and Dick in 1997 and have been identified in other forms of cancer, including the brain, breast, lung, and liver tumors. These cells also show a striking resemblance to normal stem cells, for instance, in their ability to give rise to both the progenitor and malignant cells via asymmetric mitosis. These cells act on their own and play a significant role in the progression of tumors, inducing metastatic foci and bearing chemoresistance and radiotherapy resistance to standard treatments. This resistance can be attributed to several mechanisms, including active DNA repair, non-cycling state, and efflux of the drugs. They are components of the immune system that allow them to interact with other immune cells, thus escaping any immune responses while at the same time aiding in the recurrence of the tumors. Many crucial signaling pathways in the body, such as Wnt/β-catenin, Notch, and Hedgehog, control neural stem cells' actions. New therapies have been integrated against cancer aimed at cancer stem cells, such as specific marker blocking, miRNA/LncRNA therapy, and immunotherapy. There is also great potential in new strategies, such as nanotechnology-based targeting of cancer stem cells to reduce the chances of tumor recurrence. Management techniques seek to eradicate the cancer stem cell population to mitigate the chances of recurrence and enhance treatment success.

[*] **Corresponding author Satish Ramalingam:** Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India; E-mail: satishr@srmist.edu.in

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Keywords: ALDH, Asymmetric division, Cancer heterogeneity, Cancer stem cells, Chemoresistance, Differentiation, DNA repair, Epigenetics, Epithelial-mesenchymal transition, Hedgehog pathway, Immunotherapy, Markers, Metastasis, Microenvironment, Notch pathway, Proliferation, Quiescence, Self-renewal, Tumor growth, Tumor microenvironment.

INTRODUCTION TO CANCER STEM CELLS

Cancer stem cells are small subunits of cells formed within a solid tumor that are capable of self-renewal, leading to continuous tumor growth. They are similar to normal stem cells and can divide to form undifferentiated masses of cells. The mitosis of a cancer stem cell is asymmetric and can give rise to both progenitor and malignant cells. The identification and characterization of these cells were first done by Bonnet and Dick (1997) in acute myeloid leukemia (AML) in CD34+ CD38- sets; later, cancer stem cells were also spotted in other types of tumors in the brain, breasts, lung, and liver. These stem cells, which are originally undifferentiated cells, would differentiate for the renewal of cells or tumorigenesis.

History and Evolution of Cancer Stem Cells

1997: Scientists Bonnet and John Dick identified masses of cells that would divide uncontrollably in leukemia when those cells were put in mice. They would then provide evidence that supported the hypothesis of the formation of cancer stem cells.

2000: Cancer stem cells were studied in a broader spectrum, and their existence was attributed to solid tumors that would be present in the brain, breast, and colon cancer. The solid tumors were identified when the cell samples were tested with molecular/surface markers and functional assays.

2010: Later, around 2010, researchers began looking in depth for the functional understanding of cancer stem cells. They focused on differentiating cancer stem cells from normal stem cells and their interactions with other cells, the pathways associated with the cells, and how to treat cancers that are represented by cancer stem cells.

Current Concerns and Challenges

With ongoing research on cancer stem cells, researchers have developed target therapies that work under the mechanism of targeting the specific cancer stem cell and working to eliminate them. However, cancer stem cells are very complex

structures and are heterogeneous in nature. Different cancers have different types of cancer stem cells, and to use target technology to destroy them is extremely complicated; hence, newer and more effective approaches have been developed to destroy these cells in cancerous tumors.

CHARACTERISTICS OF CANCER STEM CELLS

Cancer stem cells can be caused by differentiation and self-renewal in multipotent, tissue-specific, mature, or progenitor stem cells. In self-renewal, stem cells can continue to exist throughout an organism's lifetime, whereas in differentiation, progenitors and mature cells are passed on for regeneration purposes or tissue genesis. Differentiation is typically a one-way process, as after division, the cell loses the self-renewal property, but in the case of self-renewal in stem cells, the progenitor cells end up dividing to form mature cells and do not lose the self-renewal characteristic (Figs. **1** and **2**) [1, 2].

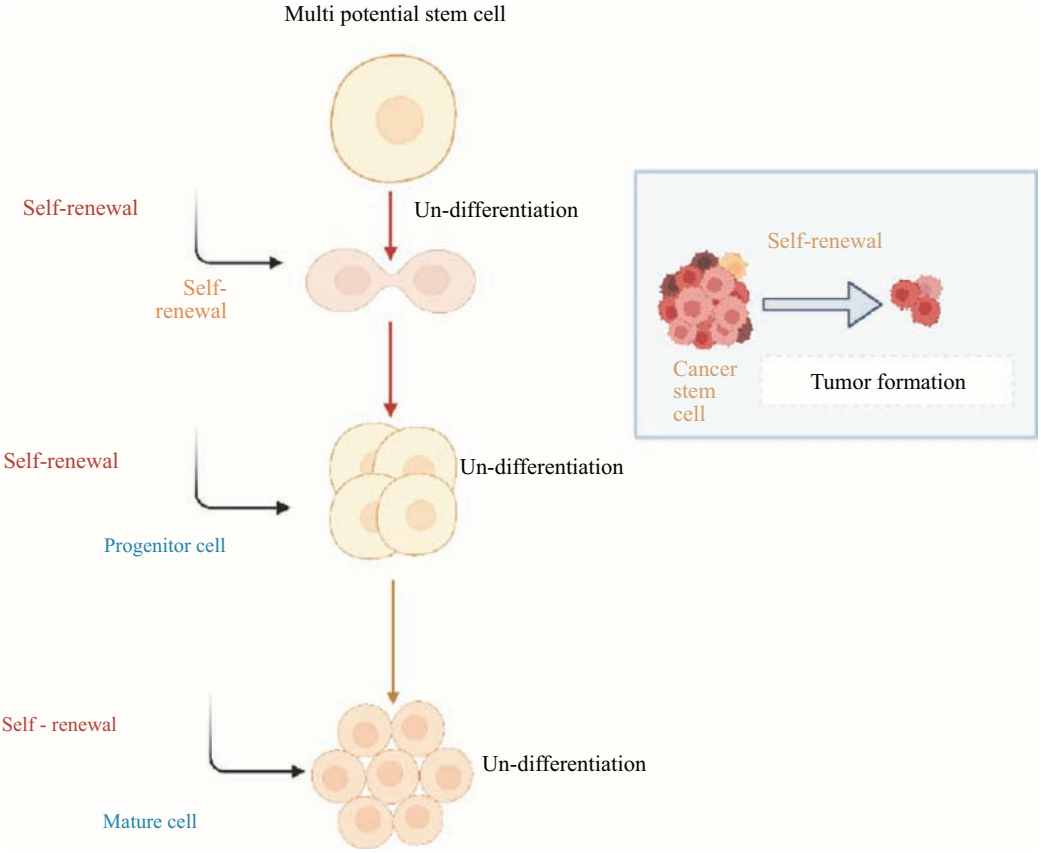

Fig. (1). Differentiation of multi-potent stem cells.

SUBJECT INDEX

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C

K.N. ArulJothi

K.N. ArulJothi did a Ph.D. in molecular and cell biology, with advanced research training from University College London (UCL) and the University of Cape Town (UCT). With over 80 scientific publications, his work spans genetics, lipid metabolism, and cancer biology, contributing significantly to understanding disease mechanisms. Currently serving as associate professor at SRM Institute of Science and Technology, Chennai, and a certified Genetic Counsellor, he integrates teaching, research, and translational science. His work bridges fundamental cell biology with precision medicine, inspiring students and advancing the application of cellular insights to improve human health and disease management.

Prakash Gangadaran

Prakash Gangadaran is a biomedical researcher and a visiting professor in the Department of Nuclear Medicine at Kyungpook National University (KNU), South Korea. His research centers work on extracellular vesicles (EVs), artificial nanovesicles, and hybrid biomimetic systems for applications in regenerative medicine, wound healing, and cancer therapy. He aims to develop innovative and clinically translatable therapeutic platforms by integrating molecular imaging, stem-cell biology, and nanotechnology. His studies emphasize mechanisms of cell communication, targeted drug delivery, and tissue regeneration. Dr. Gangadaran's work bridges basic science and translational medicine, contributing to the advancement of next-generation bio-nanotherapeutics for precision and regenerative healthcare.

Krishnan Anand

Krishnan Anand is the principal investigator in chemical pathology in the Department of Haematology and Cell Biology, School of Pathology, Faculty of Health Sciences, University of the Free State, South Africa. He leads the Precision Medicine Integrative Nano Diagnostics (P-MIND) laboratories, which focus on the biological functions of extracellular vesicles (EVs) in synthetic biology. His research encompasses cell surface protein modification, biomarker discovery through EVs derived from liquid biopsies, and the role of circulating biomarkers in disease development and stem cell biology. He has authored over 150 articles and edited eight books published by Elsevier, Springer, and Wiley. He received the National Research Foundation (NRF) rating for next generation researchers in South Africa. He was among the Top 2% of the most influential scientists worldwide in the latest list published by Stanford University. He has been serving as an editor for the eLife journal, focusing on the Africa region.

Satish Ramalingam

Satish Ramalingam is a professor in the Department of Genetic Engineering, SRM Institute of Science and Technology, Tamil Nadu, India. His research focuses on cancer biology, molecular genetics, and drug discovery. With extensive experience in teaching, mentoring, and guiding research scholars, he integrates genomic and molecular approaches to explore therapeutic interventions. He has published widely in peer-reviewed journals, books and contributed to several academic initiatives bridging genetics and biotechnology. His dedication to translational research and academic excellence continues to inspire innovation in the field of cell and molecular biology.

K. Kumaran

K. Kumaran is a geneticist and a researcher, specializing in clinical genomics, molecular diagnostics, and cancer biology. His current research focuses on clinical genetics, pharmacogenomics, and diagnostics integrating whole-exome sequencing and bioinformatics to identify genetic variants associated with familial hypercholesterolemia and related disorders. With over seven years of experience in cancer research, his work explored the small molecule inhibitors targeting cancer progression and drug cytotoxicity studies. He is dedicated to advancing personalized medicine for CVD by optimising gene panels and molecular tools for improved diagnosis and targeted therapeutics.

Kruthika Prakash

Kruthika Prakash is a researcher in molecular biology, with a focus on cancer biology, nucleolin regulation, and targeted therapeutics. Her work involves the molecular mechanisms that drive tumor development and investigates targeted strategies for effective cancer treatment. She has contributed in multiple research publications and book chapters in the areas of molecular medicine and translational oncology. Her academic interests include cancer biology, biomarker discovery, cell signalling, and the role of nucleic acids in therapeutic design. She is committed to innovative research and fostering scientific collaboration across disciplines.