

# GLYCOSYLATION AND GLYCATION IN HEALTH AND DISEASES

Editors:

**Tapan Kumar Mukherjee**

**Parth Malik**

**Ruma Rani**

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# **Glycosylation and Glycation in Health and Diseases**

Edited by

**Tapan Kumar Mukherjee**

*Amity Institute of Biotechnology  
Amity University, New Town, Kolkata  
West Bengal 700156, India*

**Parth Malik**

*School of Chemical Sciences  
Central University of Gujarat Gandhinagar  
Gujarat-382030, India*

&

**Ruma Rani**

*ICAR-National Research Centre on Equines  
Hisar-125001, Haryana, India*

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Editors: Tapan Kumar Mukherjee, Parth Malik & Ruma Rani

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## CONTENTS

PREFACE .....	i
LIST OF CONTRIBUTORS .....	iii
<b>CHAPTER 1 THE BASIC CONCEPT OF GLYCOSYLATION</b> .....	1
<i>Parth Malik, Ruma Rani and Tapan Kumar Mukherjee</i>	
<b>INTRODUCTION</b> .....	2
<b>THE ENZYMES INVOLVED IN THE PROCESS OF GLYCOSYLATION</b> .....	4
Glycosyltransferases .....	5
Glycosidases .....	8
<b>THE PROCESS OF VARIOUS TYPES OF GLYCOSYLATION</b> .....	8
N-Linked Glycosylation .....	9
Precursor Glycan Assembly and Attachment of the Assembled Glycans .....	11
Glycan Trimming in the Endoplasmic Reticulum .....	12
<i>NB</i> .....	13
Maturation of Glycans in the Golgi Apparatus .....	13
O-Linked Glycosylation .....	14
Mechanism of O-linked glycosylation .....	15
C-Linked Glycosylation .....	16
<i>NB</i> .....	16
S-Linked Glycosylation .....	16
Glypiation .....	17
Mechanism of GPI Anchored Protein Synthesis .....	17
Phosphoglycosylation .....	18
<b>THE POST-GLYCOSYLATION MODIFICATIONS</b> .....	19
• Sulfation: .....	19
• Acetylation: .....	19
• Phosphorylation: .....	19
<b>FACTORS AFFECTING GLYCOSYLATION</b> .....	19
Protein Conformation .....	20
Amino Acid Sequence .....	20
Enzyme Availability .....	20
Movement of the Proteins Through the Rough Surface ER and Golgi Apparatus .....	20
Availability of Sugars .....	21
Environmental Factors .....	22
<i>NB</i> .....	22
<b>ANALYSIS OF GLYCANS</b> .....	22
Glycan Staining and Labeling .....	23
<i>NB</i> .....	24
Affinity-Based Procedures .....	24
Saccharide Binding Proteins .....	24
Enzyme-Based Techniques .....	25
Antibody-Based Methods .....	25
Glycoprotein Purification and Enrichment .....	25
Stability of Lectins .....	26
Affinity towards Various Sugars .....	26
Affinity towards Fluorophores, Horseradish Peroxidase, And Biotin .....	26
Commercial Liability of Lectin .....	26
Glycome and Glycoproteome Analysis .....	27
Glycan Analysis by Mass Spectrometry .....	28

Glycan Analysis Using Chromatography .....	28
<b>DEGLYCOSYLATION AND ITS IMPORTANCE</b> .....	29
Enzymatic Cleavage of Glycans .....	30
<i>NB</i> .....	31
Chemical Removal of Glycans .....	31
$\beta$ -Elimination .....	32
Hydrazinolysis .....	32
<b>BIOLOGICAL IMPORTANCE OF GLYCOSYLATION</b> .....	32
Importance of Glycosylation in Protein Targeting .....	33
Importance of Glycosylation in Preventing Protein Degradation .....	33
Importance of Glycosylation in Recognition and Receptor Functions .....	34
Importance of Glycosylation in Sustaining Immune Function .....	34
<b>CONCLUSION</b> .....	36
<b>REFERENCES</b> .....	37
<b>CHAPTER 2 VITAL FUNCTIONS OF GLYCANS IN THE BIOLOGICAL SYSTEMS</b> .....	40
<i>Ruma Rani, Parth Malik, Raj Singh, Raman Kumar, Vishal Haribhai Patel and Tapan Kumar Mukherjee</i>	
<b>INTRODUCTION</b> .....	41
<b>STRUCTURAL AND MODULATORY ROLE OF GLYCANS</b> .....	45
<b>ROLE OF GLYCANS IN MEMBRANE ORGANIZATION AND FUNCTIONS</b> .....	47
<b>ROLE OF GLYCANS IN EXTRACELLULAR MATRIX ORGANIZATION</b> .....	48
<b>GLYCANS IMPART PHYSICAL STRENGTH AND PROTECTION OF BIOLOGICAL STRUCTURES</b> .....	50
<b>ROLE OF GLYCANS IN THE PROTECTION OF BIOLOGICAL STRUCTURES FROM PROTEASES</b> .....	51
<b>ROLE OF GLYCANS IN THE PHYSICAL EXPULSION OF PATHOGENS</b> .....	53
<b>ROLE OF GLYCANS IN MODULATING CELL ADHESION</b> .....	54
<b>ROLE OF GLYCANS IN DEPOT FUNCTIONS</b> .....	56
<b>ROLE OF GLYCANS IN GRADIENT GENERATION</b> .....	56
<b>ROLE OF GLYCANS TO INFLUENCE DIFFUSION BARRIERS</b> .....	57
<b>ROLE OF GLYCANS IN SOLUBILIZATION AND LUBRICATION OF BIOLOGICAL MOLECULES</b> .....	58
<b>ROLE OF GLYCANS IN THE MODULATION OF MEMBRANE RECEPTOR SIGNALING</b> .....	59
<b>ROLE OF GLYCANS IN EPIGENETIC MODIFICATION OF HISTONES AND NON-HISTONE NUCLEAR PROTEINS</b> .....	61
<b>GLYCANS IN INTRASPECIES RECOGNITION</b> .....	62
<b>GLYCANS IN INTRACELLULAR GLYCOPROTEIN FOLDING AND DEGRADATION</b> .....	63
<b>GLYCANS IN INTRACELLULAR GLYCOPROTEIN TRAFFICKING</b> .....	64
<b>GLYCANS IN TRIGGERING OF ENDOCYTOSIS AND PHAGOCYTOSIS</b> .....	64
<b>GLYCANS IN INTERSPECIES RECOGNITION</b> .....	66
<b>GLYCANS IN MICROBIAL ADHESIONS</b> .....	67
<b>GLYCANS IN RECOGNITION OF PATHOGEN-ASSOCIATED MOLECULAR PATTERNS</b> .....	68
<b>VIRAL RECOGNITION OF GLYCAN TARGETS</b> .....	68
<b>ANTIGEN RECOGNITION, UPTAKE AND PROCESSING</b> .....	69
<b>CONCLUSION</b> .....	69
<b>REFERENCES</b> .....	70
<b>CHAPTER 3 UNDERSTANDING CONGENITAL GLYCOSYLATION DISORDERS</b> .....	84
<i>Himel Mondal, Shaikat Mondal and Rajeev K. Singla</i>	

<b>INTRODUCTION</b> .....	84
<b>CAUSES OF CONGENITAL DISORDER OF GLYCOSYLATION</b> .....	86
Protein N-Glycosylation .....	86
Protein O-Glycosylation .....	87
Lipid Glycosylation .....	87
Other Glycosylation Pathways .....	87
<i>Genetic Mutations</i> .....	87
<i>Enzyme Deficiencies</i> .....	88
<i>Transporter Deficiencies</i> .....	88
<i>Complex Molecular Pathways</i> .....	89
<b>SIGNS AND SYMPTOMS OF CONGENITAL DISORDER OF GLYCOSYLATION</b> .....	90
Developmental Delays and Intellectual Disabilities .....	90
Seizures .....	91
Hypotonia and Muscle Weakness .....	91
Gastrointestinal Issues .....	92
Coagulation Abnormalities .....	92
Dysmorphic Features .....	92
Failure to Thrive .....	93
Visceral Organ Involvement .....	93
Other Neurological Symptoms .....	93
Hearing and Vision Impairments .....	94
Immune System Dysregulation .....	94
<b>TESTING AND DIAGNOSIS FOR CONGENITAL DISORDER OF GLYCOSYLATION</b> .....	95
Clinical Evaluation .....	95
Biochemical Testing .....	95
Genetic Testing .....	96
Neuroimaging and Organ-specific Evaluations .....	97
<b>DISORDERS OF PROTEIN N-GLYCOSYLATION</b> .....	97
Features of N-glycosylation Defects .....	97
Defects in Endoplasmic Reticulum N-glycosylation .....	99
Defects in Golgi N-glycosylation .....	100
Disorders of N-glycoprotein Deglycosylation .....	100
<b>DISORDERS OF PROTEIN O-GLYCOSYLATION</b> .....	101
Defects in O-man Synthesis (Congenital Muscular Dystrophies) .....	102
Defects in O-GalNAc Synthesis .....	103
Defects in other O-glycosylation Families .....	104
<b>DEFECTS IN GLYCOSAMINOGLYCAN (GAG) SYNTHESIS</b> .....	106
Specific GAG Synthesis Disorders .....	107
<b>DEFECTS IN LIPID AND GPI-ANCHOR GLYCOSYLATION</b> .....	108
Defects in GPI-anchored Proteins .....	108
Defects in Glycosphingolipid (GSL) Synthesis .....	109
<b>DEFECTS OF MULTIPLE GLYCOSYLATION AND OTHER PATHWAYS</b> .....	111
Defects in the Synthesis of Sugar Precursors .....	111
Defects in the Biosynthesis of Dolichol-monosaccharides .....	113
Defects in Golgi Homeostasis .....	113
<b>OVERCOMING THE DEFECTS/TREATMENT OF GLYCOSYLATION</b> .....	114
Genetic Counseling and Diagnosis .....	114
Supportive Care and Symptomatic Management .....	114
Emerging Therapeutic Approaches .....	115
Multidisciplinary Management .....	115
<b>CONCLUSION</b> .....	116

<b>REFERENCES</b> .....	116
<b>CHAPTER 4 THE BIOLOGY OF ADVANCED GLYCATION END PRODUCTS</b> .....	120
<i>Parth Malik, Ruma Rani and Tapan Kumar Mukherjee</i>	
<b>INTRODUCTION</b> .....	121
<b>STEPS OF FORMATION OF ADVANCED GLYCATION END PRODUCTS</b> .....	125
<b>FACTORS AFFECTING ADVANCED GLYCATION END-PRODUCT FORMATION</b> ....	128
The Exogenous Factors Affecting Advanced Glycation End Products Formation .....	129
Processed Food and Diet .....	130
Ultraviolet Light and Ionizing Radiations .....	131
Cigarette Smoking and Air Pollution .....	131
The Endogenous Factors Affecting Advanced Glycation End Products Formation .....	132
<i>Hyperglycemia</i> .....	132
<i>Aging</i> .....	132
<i>Obesity</i> .....	134
Chronic Renal Insufficiency .....	135
Glyoxalase I Deficiency .....	136
Autoimmune and Inflammatory Conditions support Advanced Glycation End-product Formation .....	137
<b>STRUCTURAL DISTINCTIONS OF VARIOUS ADVANCED GLYCATION END PRODUCTS</b> .....	137
<b>MEASUREMENT OF ADVANCED GLYCATION END PRODUCTS</b> .....	141
Spectrofluorimetric Methods .....	148
Quantification of Advanced Glycation End Products from serum .....	149
Detection of Serum and Urine Small-sized Advanced Glycation End products Peptides using Flow Injection Assay .....	149
Western-Blotting Mediated Detection of Advanced Glycation End products .....	149
Advanced Glycation End Products-Modified Proteins in Dot-Immunobinding Assay .....	150
<b>THE BINDING PROTEINS OF ADVANCED GLYCATION END PRODUCTS</b> .....	150
Receptor For Advanced Glycation End Product .....	151
The Advanced Glycation End Products-Receptor (AGE-R) Complex .....	152
Macrophage Scavenger Receptor Family .....	154
<b>THE EFFECTS OF ADVANCED GLYCATION END PRODUCTS ON CELL SIGNALING MOLECULES</b> .....	157
<b>THE EPIGENETIC EFFECTS OF ADVANCED GLYCATION END PRODUCTS</b> .....	159
<b>RECEPTOR TRAFFICKING AND INTRACELLULAR PROTEOLYSIS OF ADVANCED GLYCATION END PRODUCTS</b> .....	162
<b>IMPLICATION OF GLYCATION IN HUMAN PATHOPHYSIOLOGY</b> .....	164
Biological Consequences of Advanced Glycation End Products Generation in the Human Body .....	164
The Intracellular Proteins .....	165
Extracellular Proteins .....	165
Nucleic Acids .....	166
Other Pathological Outcomes .....	168
Pathological Effects of Advanced Glycation End Products .....	168
Effects of Glycation on Serological Activities, Visual Health, and Dermal Functioning .....	169
(i) <i>In the Blood</i> .....	169
(ii) <i>On the Eye Lens</i> .....	169
(iii) <i>On the Dermal Locations</i> .....	170
Reactivity of Advanced Glycation End products .....	170
Clearance of Advanced Glycation End products .....	170

<b>COMPARATIVE ANALYSIS OF GLYCOSYLATION VERSUS GLYCATION</b> .....	172
Materials Used in Glycosylation Versus Glycation .....	172
Functional Sites of Glycosylation Versus Glycation .....	172
Process of Glycosylation Versus Glycation .....	173
<i>Enzymatic Versus Non-Enzymatic Reactions</i> .....	173
Effects of Glycosylation Versus Glycation on Various Human Systems .....	173
• <i>N-linked glycosylation</i> .....	174
• <i>O-linked glycosylation:</i> .....	174
• <i>Phosphoserine glycosylation</i> .....	174
• <i>C-manipulation</i> .....	174
• <i>Glypiation</i> .....	175
<b>THE PHARMACOLOGICAL INTERVENTION OF ADVANCED GLYCATION END PRODUCTS: THE ANTI-ADVANCED GLYCATION END PRODUCT MOLECULES</b> ....	175
Pharmacological Interventions of Advanced Glycation End Products .....	175
<b>CONCLUSION</b> .....	177
<b>REFERENCES</b> .....	179

<b>CHAPTER 5 RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS IN HEALTH AND PHYSIOLOGY</b> .....	190
<i>Ruma Rani, Parth Malik and Tapan Kumar Mukherjee</i>	
<b>INTRODUCTION</b> .....	191
<b>CHARACTERIZATION OF RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS GENE</b> .....	192
<b>CHARACTERIZATION OF RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS PROTEIN AND ITS SOLUBLE FORMS</b> .....	194
<b>THE LIGANDS OF RECEPTORS FOR ADVANCED GLYCATION END PRODUCTS</b> ...	197
<b>ADVANCED GLYCATION END PRODUCTS (AGES)</b> .....	199
High Mobility Group Box Protein 1 (HMGB1) .....	200
The HMG proteins are subdivided into the following 3 superfamilies: .....	200
<i>HMGA</i> .....	200
<i>HMGB</i> .....	200
<i>HMGN:</i> .....	200
<i>HMGB1:</i> .....	200
The High-Mobility Group Gene and Protein .....	201
A typical HMGB1 polypeptide chain consists of the following: .....	201
<i>HMG box A</i> .....	201
<i>HMG box B</i> .....	201
<i>Acidic C Terminus</i> .....	201
Sub-cellular Localization and Cellular Release of High-Mobility Group Box Protein .....	203
The most generalized HMGB1 locations are as under: .....	203
The Nuclear High Mobility Group Box Protein 1 .....	204
<i>NB</i> .....	204
The Cytoplasmic High Mobility Group Box Protein 1 .....	204
Nuclear to Cytoplasmic Translocation of High Mobility Group Box Protein 1 .....	204
Cytoplasmic to Extracellular Space Release of High Mobility Group Box Protein 1 .....	205
The Endosomal/Lysosomal High Mobility Group Box Protein 1 .....	206
The Mitochondrial High Mobility Group Box Protein 1 .....	206
The Membrane-bound High Mobility Group Box Protein 1 .....	209
The Extracellular High Mobility Group Box Protein 1 .....	210
Functions of High Mobility Group Box Protein 1 .....	212
Nuclear Functions of High Mobility Group Box Protein 1 .....	213

Role of High Mobility Group Box Protein 1 in Gene Regulation .....	213
Role of High Mobility Group Box Protein 1 in Repairing the Damaged DNA .....	213
Role of High Mobility Group Box Protein 1 in Antibody Diversity .....	213
Other Nuclear HMGB1 Functions of High Mobility Group Box Protein 1 .....	214
<i>Multiple independent studies described the following functions of HMGB1:</i> .....	214
Cytoplasmic Functions of High Mobility Group Box Protein 1 .....	214
• <i>TLR9 Mediated High Mobility Group Box Protein 1 Activities</i> .....	214
• <i>Autophagic Actions of High Mobility Group Box Protein 1</i> .....	214
Functions of HMGB1 in the Extracellular Compartment .....	214
Pathophysiology of High Mobility Group Box Protein 1 .....	215
S100/CALGRANULIN FAMILY .....	216
Structure of S100 proteins .....	220
Functions of S100 proteins .....	220
Pathology Related to S100 Proteins .....	220
<b>LYSOPHOSPHATIDIC ACID</b> .....	220
<b>OLIGOMERIC FORMS OF AMYLOID-B PEPTIDE</b> .....	222
A $\beta$ Oligomers .....	223
<b>ISLET AMYLOID POLYPEPTIDE</b> .....	224
<b>THE PHYSIOLOGICAL ROLE OF RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS</b> .....	225
Thus, the physiological role of RAGE is discussed in the following sections: .....	226
<i>Role of Receptor for Advanced Glycation End Products in Embryogenesis</i> .....	226
<i>Role of Receptor for Advanced Glycation End Products in Lung Homeostasis</i> .....	226
<i>Role of Receptor for Advanced Glycation End Products in Bone Morphogenesis</i> .....	227
<i>Role of Receptor for Advanced Glycation End Products in Neurite Outgrowth</i> .....	227
<i>Role of Receptor for Advanced Glycation End Products in Innate Immunity</i> .....	228
<b>THE PATHOPHYSIOLOGICAL ROLE OF RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS</b> .....	229
<b>CONCLUSION</b> .....	230
<b>REFERENCES</b> .....	231

<b>CHAPTER 6 RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS AS A MEDIATOR OF INFLAMMATION AND OXIDATIVE STRESS</b> .....	240
<i>Ruma Rani, Parth Malik and Tapan Kumar Mukherjee</i>	
<b>INTRODUCTION</b> .....	241
<b>RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS AS MEDIATORS OF INFLAMMATION</b> .....	243
<b>RAGE AS A REGULATOR OF INNATE IMMUNITY</b> .....	245
<b>RAGE AS A REGULATOR OF ADAPTIVE IMMUNITY</b> .....	247
<b>LEUKOCYTE RECRUITMENT AND INFLAMMATION AS MEDIATOR OF RAGE-DEPENDENT ACTION</b> .....	248
<b>TRANSCRIPTION FACTORS AS MEDIATORS OF RAGE-DEPENDENT INFLAMMATION</b> .....	250
<b>RAGE AS A MEDIATOR OF OXIDATIVE STRESS</b> .....	251
<b>ROLE OF MITOCHONDRIA IN RAGE-DEPENDENT REACTIVE OXYGEN SPECIES GENERATION</b> .....	254
<b>INVOLVEMENT OF NADPH OXIDASE IN RAGE-MEDIATED ROS GENERATION</b> .....	258
<b>THE GENERATION OF OXIDATIVE STRESS BY HIGH LEVEL OF REACTIVE OXYGEN SPECIES</b> .....	260
<b>THE ANTIOXIDANT SYSTEM AND REGULATION OF OXIDATIVE STRESS</b> .....	261
<b>ANTIOXIDANT ENZYMES AND THEIR WORKING MECHANISMS</b> .....	261

NON-ENZYMATIC ANTIOXIDANTS AND THEIR ACTION MECHANISMS .....	270
NATURAL ANTIOXIDANTS .....	271
RELATIONSHIP OF PRO-INFLAMMATORY REACTIONS AND OXIDATIVE STRESS .....	272
OXIDATIVE STRESS AND INFLAMMATION AS MEDIATORS OF VARIOUS RAGE-DEPENDENT DISEASE COMPLICATIONS .....	274
CONCLUSION .....	277
REFERENCES .....	278
<b>CHAPTER 7 RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS IN PULMONARY DISEASES .....</b>	<b>286</b>
<i>Parth Malik, Ruma Rani and Tapan Kumar Mukherjee</i>	
<b>INTRODUCTION .....</b>	<b>287</b>
<b>CELL-SPECIFIC EXPRESSION OF RAGE IN THE LUNG TISSUES .....</b>	<b>288</b>
<b>THE PHYSIOLOGICAL ROLE OF RAGE IN THE LUNG TISSUES .....</b>	<b>289</b>
<b>THE PATHOPHYSIOLOGICAL ROLE OF RAGE IN THE COMPLICATION OF LUNG-ASSOCIATED DISEASES .....</b>	<b>290</b>
<b>ROLE OF RAGE IN THE COMPLICATION OF ASTHMA .....</b>	<b>290</b>
<b>CONSEQUENCES OF RAGE EXPRESSION IN ASTHMA COMPLICATIONS .....</b>	<b>291</b>
<b>LIGAND-RAGE INTERACTIONS INVOLVED IN ASTHMATIC COMPLICATIONS .....</b>	<b>291</b>
<b>ROLE OF SOLUBLE RAGE IN THE COMPLICATION OF ASTHMA .....</b>	<b>292</b>
<b>ROLE OF RAGE IN THE CHRONIC OBSTRUCTIVE PULMONARY DISEASE .....</b>	<b>292</b>
<b>CONSEQUENCES OF RAGE EXPRESSION IN AGGRAVATED CHRONIC OBSTRUCTIVE PULMONARY DISEASE COMPLICATIONS .....</b>	<b>292</b>
<b>LIGANDS-RAGE INTERACTION IN THE COMPLICATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE .....</b>	<b>293</b>
<b>ROLE OF SOLUBLE RAGE IN THE COMPLICATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE .....</b>	<b>294</b>
<b>ROLE OF RAGE IN THE COMPLICATION OF ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME .....</b>	<b>294</b>
<b>LUNG DAMAGE ASSOCIATED WITH RAGE EXPRESSION .....</b>	<b>295</b>
<b>RAGE-LIGAND INTERACTION IN THE COMPLICATION OF ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME .....</b>	<b>295</b>
<b>ROLE OF SOLUBLE RAGE IN INACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME .....</b>	<b>297</b>
<b>ROLE OF RAGE IN THE COMPLICATION OF IDIOPATHIC PULMONARY FIBROSIS .....</b>	<b>298</b>
<b>LIGAND-RAGE INTERACTIONS IN IDIOPATHIC PULMONARY FIBROSIS .....</b>	<b>298</b>
<b>ROLE OF SOLUBLE RAGE IN IDIOPATHIC PULMONARY FIBROSIS .....</b>	<b>303</b>
<b>ROLE OF RAGE IN THE COMPLICATION OF CYSTIC FIBROSIS .....</b>	<b>303</b>
<b>LIGAND-RAGE INTERACTIONS IN CYSTIC FIBROSIS COMPLICATION .....</b>	<b>303</b>
<b>ROLE OF RAGE IN THE COMPLICATION OF BRONCHIOLITIS .....</b>	<b>306</b>
<b>RELATIONSHIP OF RAGE AND SRAGE WITH BRONCHIOLITIS .....</b>	<b>306</b>
<b>ROLE OF RAGE IN THE COMPLICATION OF SEPSIS .....</b>	<b>307</b>
<b>LIGAND-RAGE INTERACTIONS IN SEPSIS COMPLICATION .....</b>	<b>307</b>
<b>ROLE OF RAGE IN THE COMPLICATION OF PULMONARY ARTERIAL HYPERTENSION .....</b>	<b>308</b>
<b>LIGAND-RAGE INTERACTIONS IN THE COMPLICATION OF PULMONARY ARTERIAL HYPERTENSION .....</b>	<b>308</b>
<b>ROLE OF RAGE IN TRAUMATIC BRAIN INJURY MEDIATED PULMONARY DYSFUNCTION AND LUNG TRANSPLANTATION REJECTION .....</b>	<b>309</b>

INVOLVEMENT OF LIGAND-RAGE INTERACTIONS IN TRANSPLANTATION	
REJECTION .....	309
ANTI-RAGE THERAPY AGAINST VARIOUS PULMONARY DISEASES .....	310
CONCLUSION .....	317
REFERENCES .....	318
<b>CHAPTER 8 RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS IN</b>	
<b>CARDIOVASCULAR AND DIABETIC COMPLICATION(S)</b> .....	326
<i>Ruma Rani, Parth Malik and Tapan Kumar Mukherjee</i>	
INTRODUCTION .....	327
GLYCATED PROTEINS AS A MODEL OF TISSUE INJURY LINKED TO DIABETES	
MELLITUS AND AGING .....	329
RELATIONSHIP OF CARDIOVASCULAR COMPLICATION AND DIABETES .....	331
ROLE OF RAGE IN ATHEROSCLEROSIS .....	331
ATHEROSCLEROSIS-RELATED STUDIES IN HUMAN SUBJECTS .....	333
ATHEROSCLEROSIS-RELATED STUDIES IN ANIMAL MODELS .....	334
ROLE OF RAGE IN PERIPHERAL ARTERIAL DISEASE .....	335
PERIPHERAL ARTERIAL DISEASE-RELATED STUDIES IN HUMAN SUBJECTS .....	335
PERIPHERAL ARTERIAL DISEASE-RELATED STUDIES IN ANIMAL MODELS .....	336
ROLE OF RAGE IN ATRIAL FIBRILLATION .....	337
ROLE OF RAGE IN THROMBOTIC DISORDERS .....	338
THROMBOTIC DISORDERS RELATED STUDIES IN HUMAN SUBJECTS .....	338
THROMBOTIC DISORDERS RELATED STUDIES IN ANIMAL MODELS .....	339
ROLE OF RAGE IN MYOCARDIAL INFARCTION .....	340
MYOCARDIAL INFARCTION-RELATED STUDIES IN HUMAN SUBJECTS .....	340
MYOCARDIAL INFARCTION-RELATED STUDIES IN ANIMAL MODELS .....	342
ROLE OF RAGE IN VASCULAR CALCIFICATION .....	343
VASCULAR CALCIFICATION-RELATED STUDIES IN HUMAN SUBJECTS .....	343
VASCULAR CALCIFICATION-RELATED STUDIES IN ANIMAL MODELS .....	344
ROLE OF RAGE IN DIABETES-ASSOCIATED CARDIAC FIBROSIS .....	344
ROLE OF RAGE IN OBESITY AND DIABETES .....	345
ROLE OF RAGE IN DIABETIC NEUROPATHY .....	347
ROLE OF RAGE IN DIABETIC RETINOPATHY .....	350
ROLE OF RAGE IN DIABETIC NEPHROPATHY .....	353
CONCLUSION .....	355
REFERENCES .....	355
<b>CHAPTER 9 RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS IN VARIOUS</b>	
<b>TYPES OF CANCERS</b> .....	369
<i>Parth Malik, Ruma Rani and Tapan Kumar Mukherjee</i>	
INTRODUCTION .....	369
RAGE LIGANDS IN THE DEVELOPMENT AND PROGRESSION OF CANCERS .....	372
RAGE IN THE PROTECTION AGAINST LUNG CANCER DEVELOPMENT AND	
PROGRESSION .....	375
RAGE IN THE PROTECTION VERSUS PROMOTION AGAINST LUNG CANCER .....	379
RAGE GENE POLYMORPHISM IN LUNG CANCER DEVELOPMENT AND	
PROGRESSION .....	380
RAGE IN THE DEVELOPMENT AND PROGRESSION OF CANCERS OTHER THAN	
LUNG CANCERS .....	381
CELLULAR PROCESSES INVOLVED IN THE RAGE-DEPENDENT CANCER	
DEVELOPMENT AND PROGRESSION .....	382
RAGE IN CANCER CELL PROLIFERATION .....	383

<b>RAGE IN CANCER CELL SURVIVAL AND AUTOPHAGY</b> .....	384
<b>RAGE IN CANCER CELL ANGIOGENESIS</b> .....	386
<b>RAGE IN CANCER CELL APOPTOSIS</b> .....	386
<b>RAGE IN CANCER CELL INVASION AND METASTASIS</b> .....	387
<b>MECHANISM OF RAGE-DEPENDENT CANCER CELL DEVELOPMENT AND PROGRESSION</b> .....	387
• ChREBP: .....	389
• JAK/STAT3: .....	389
• MAPKs and MMPs: .....	390
• Nrf-2 .....	390
• PI3K/Akt .....	390
• Beclin-1 .....	391
• MAPK .....	392
• MicroRNA .....	392
• MMPs .....	393
• NF-κB/Snail .....	393
• PI3K/Akt .....	393
• Angiogenesis .....	395
• MAPKs .....	395
• MMPs .....	395
• NF-κB .....	395
• p53 .....	396
• PI3K/Akt/mTOR .....	396
• STAT3 .....	396
<b>CONCLUSION</b> .....	396
<b>REFERENCES</b> .....	397

<b>CHAPTER 10 RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS IN NEURONAL PATHOPHYSIOLOGY</b> .....	408
<i>Parth Malik, Ruma Rani and Tapan Kumar Mukherjee</i>	
<b>INTRODUCTION</b> .....	409
<b>RAGE EXPRESSION IN NEURONAL AND SUPPORTING CELLS</b> .....	410
<b>RAGE LIGANDS IN NEURONAL AND SUPPORTING CELLS</b> .....	413
<b>AMYLOID BETA PEPTIDE IN NEURONAL CELLS</b> .....	413
<b>HMGB1 IN NEURONAL CELLS</b> .....	416
<b>S100. IN NEURONAL CELLS</b> .....	419
<b>STRUCTURAL DISTINCTIONS OF S100B-RAGE LIGANDS</b> .....	419
<b>ADVANCED GLYCATION END PRODUCTS IN NEURONAL CELLS</b> .....	424
<b>ROLE OF RAGE IN NEURONAL GROWTH AND DIFFERENTIATION</b> .....	426
<b>THE PATHOPHYSIOLOGICAL ROLE OF RAGE IN THE NERVOUS SYSTEM</b> .....	427
<b>ROLE OF RAGE IN THE COMPLICATION OF ALZHEIMER'S DISEASE</b> .....	429
<b>ROLE OF RAGE IN THE COMPLICATION OF PARKINSON'S DISEASE</b> .....	432
<b>ROLE OF RAGE IN THE COMPLICATION OF HUNTINGTON'S DISEASE</b> .....	433
<b>ROLE OF RAGE IN AMYOTROPHIC LATERAL SCLEROSIS</b> .....	434
<b>ROLE OF RAGE IN CREUTZFELDT-JAKOB'S DISEASE</b> .....	435
<b>ROLE OF RAGE IN PERIPHERAL NEUROPATHIES</b> .....	436
<b>ROLE OF RAGE IN FAMILIAL AMYLOID NEUROPATHY</b> .....	436
<b>ROLE OF RAGE IN SPINAL CORD INJURY</b> .....	437
<b>ROLE OF RAGE IN EPILEPSY</b> .....	438
<b>THE ANTI-RAGE MOLECULES AGAINST NEUROLOGICAL DISEASES</b> .....	439
<b>CONCLUSION</b> .....	445

<b>REFERENCES</b> .....	446
<b>SUBJECT INDEX</b> .....	682

## PREFACE

The book titled, “Glycosylation and Glycation in Health and Diseases” is hereby planned to be completed in 10 chapters. While glycosylation is a physiological process engrossing glycoprotein and glycolipid synthesis via enzyme-assisted carbohydrates’ addition to proteins and lipids respectively; glycation is a pathophysiological process where excess carbohydrates are added to the proteins via biochemical reactions without the involvement of any enzymes.

The book commences with an introductory chapter describing various aspects of glycosylation. Subsequently, each chapter is dedicated to the biological roles of glycosylated molecules and various aspects of congenital disorders associated with glycosylation, respectively. In the domain of glycation, one chapter describes the generation of advanced glycation end products (AGEs) and their effects on various mammalian life-sustaining events. Subsequently, five chapters illustrate the pathophysiological effects of the receptor for advanced glycation end products (RAGE) on various organs, about health concerns. Finally, one chapter is dedicated to the pro-inflammatory and pro-oxidative mechanisms through which RAGE complicates various diseased conditions. Thereby, the mechanistic and pathophysiological aspects of both glycosylation and glycation are comprehensively attempted for the first time, in this book.

The study of glycans or carbohydrates has emerged as a necessity for the undergraduate and graduate syllabi of various Life Sciences related subjects, including cell biology, biochemistry, molecular biology, biotechnology, microbiology, immunology (host-pathogen interaction), and others. The fundamental biomolecular aspects have therein propelled glycation and glycosylation as major research themes in the biopharmaceutical and biotechnological industry including new drug discoveries against various cancers. Considering the prominent functions of glycans vis-à-vis immune interactions, conjugated carbohydrates are being promptly screened as next-generation therapeutics, vaccines, and diagnostic augmenters.

Closing in on the footmarks of glycosylation, the study of glycation has swiftly emerged as an essential aspect of current research, considering the awareness of physical stress as a deteriorating health feature in developed and developing economies. The biology of glycation is one of the most evolving areas of present-day “Molecular Medicine” research. It is now widely accepted that the interaction of AGEs with RAGE enhances inflammatory and oxidative stress. This enhanced level of inflammation and oxidative stress propagates various non-communicable disorders, including diabetes, cardiovascular, pulmonary, and vascular complications, associated with major organs, viz. kidney, liver, pancreas, and nervous system. At present, the glycated haemoglobin *i.e.* HBA1c in the RBC is recognized as a decisive hallmark of diabetes, being in regular use for diagnosis. Finally, AGE-RAGE interaction aggravated extents of inflammation and oxidative stress complicates various cancers. Thus, studies probing the therapeutic usefulness of anti-AGE/anti-RAGE molecules against senescence and aging are being conducted with increasing reliability. Concerning this, every year thousands of manuscripts are published on “Glycosylation and Glycation”, across the globe. Essentially, not only the students and teachers but also the glycobiology researchers too, would substantially benefit from this book, which in due course, would cement its place in many libraries as well as laboratories.

**Tapan Kumar Mukherjee**  
Department of Biotechnology  
Amity University, New Town, Kolkata

West Bengal 700156, India  
**Parth Malik**  
School of Chemical Sciences  
Central University of Gujarat Gandhinagar  
Gujarat-382030, India

&

**Ruma Rani**  
ICAR-National Research Centre on Equines  
Hisar-125001, Haryana, India

## List of Contributors

- Himel Mondal** Department of Physiology, All India Institute of Medical Sciences, Deoghar, Jharkhand-814152, India
- Parth Malik** School of Chemical Sciences, Central University of Gujarat, Gandhinagar, Gujarat-382030, India  
Swarnim Startup & Innovation University, Bhoyan-Rathod, Gandhinagar-Gujarat, India
- Ruma Rani** ICAR-National Research Centre on Equines, Hisar-125001, Haryana, India
- Raj Singh** Department of Biotechnology, Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala, Haryana 133207, India
- Raman Kumar** Department of Biotechnology, Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala, Haryana 133207, India
- Rajeev K. Singla** Joint Laboratory of Artificial Intelligence for Critical Care Medicine, Department of Critical Care Medicine and Institutes for Systems Genetics, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu, China
- Shaikat Mondal** Department of Physiology, Raiganj Government Medical College and Hospital, Raiganj, West Bengal, India
- Tapan Kumar Mukherjee** Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India
- Vishal Haribhai Patel** Institute of Biotechnology, Amity University, Noida-201301, Uttar Pradesh, India

## The Basic Concept of Glycosylation

Parth Malik<sup>1,2,†</sup>, Ruma Rani<sup>3,†</sup> and Tapan Kumar Mukherjee<sup>4,\*</sup>

<sup>1</sup> School of Chemical Sciences, Central University of Gujarat, Gandhinagar, Gujarat-382030, India

<sup>2</sup> Swarnim Startup & Innovation University, Bhoyan-Rathod, Gandhinagar-Gujarat, India

<sup>3</sup> ICAR-National Research Centre on Equines, Hisar-125001, Haryana, India

<sup>4</sup> Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India

**Abstract:** Glycobiology aims at structure-function correlational analysis of carbohydrates (sugar or glycan). A monosaccharide is the simplest form of carbohydrate that no longer be hydrolyzed. The other forms of carbohydrates are formed by glycosidic linkages of monosaccharides, such as disaccharides, oligosaccharides, and polysaccharides, comprising two, three to ten, and more than ten monosaccharides, respectively. Carbohydrates act as one of the major energy sources (*e.g.*, ATP) and are also involved in cellular protection, stabilization, organization, and barrier functions. In the cellular system, carbohydrates are present in pure and protein-conjugated forms, which are referred to as glycoproteins. Conjugated carbohydrates are also present in the form of glycolipids and proteoglycans. Notably, *N- and O-linked* glycosylation as major forms occur in the rough surface endoplasmic reticulum (RER) and Golgi apparatus respectively, adding carbohydrates to proteins and thus making glycoproteins. Relatively fewer common types of glycosylation are the *C-linked* glycosylation, *S-linked* glycosylation, glypiation, and phosphoglycosylation. A complex interplay of two enzyme groups such as glycosyl transferases (adding carbohydrates to proteins) and glycosidases/glycosyl hydrolases (removing carbohydrates from proteins) control the glycosylation extent. Prominent cellular factors regulating glycosylation are the availability of carbohydrates, proteins, enzymes, movement of proteins from RER to Golgi, and several other environmental factors regulating post-translational modifications. This chapter describes the various aspects of glycobiology including protein glycosylation, purification, and analysis of glycans, and their role in physiology and pathophysiology.

\* **Corresponding author Tapan Kumar Mukherjee:** Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India; E-mail: tapan400@gmail.com

† These authors contributed equally to this work.

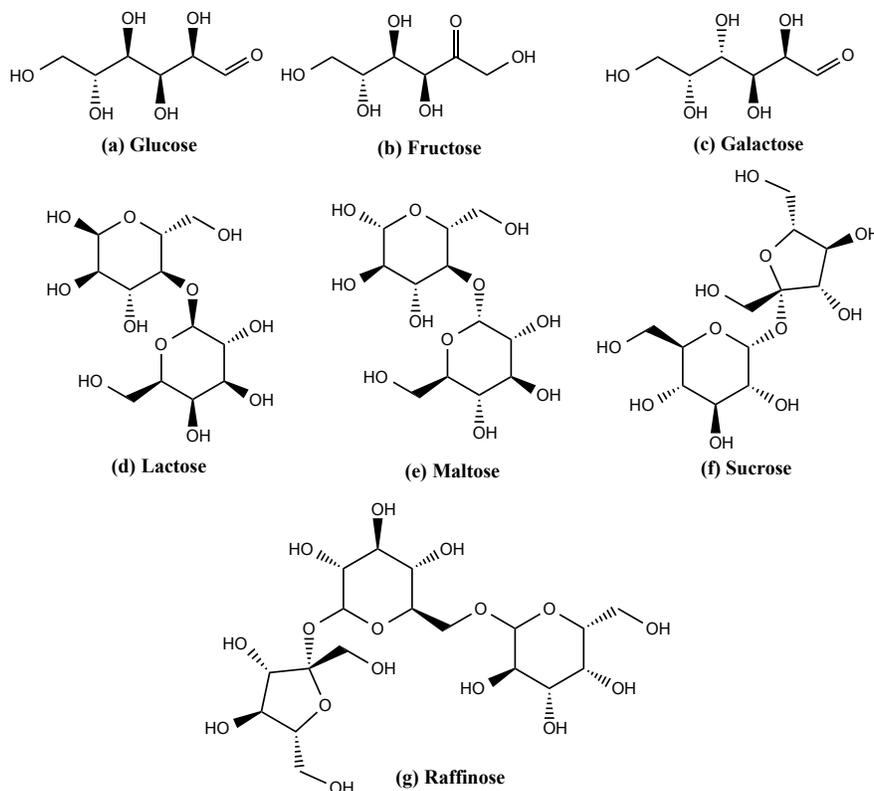
**Keywords:** Glycobiology, Glycosylation, Glycoproteins, Glycosyltransferases, Glypiation, Glycan analysis, Glycosidases/glycosyl hydrolases, *N*-linked glycosylation, *O*-linked glycosylation, Phosphoglycosylation, *S*-linked glycosylation.

## INTRODUCTION

The study of structure, functions, and biological aspects of saccharides (carbohydrates, sugar chains, or glycans) is called “Glycobiology”. The generic term for carbohydrate is interchangeable with sugar (the sweet-tasting carbohydrate) or glycans (compounds containing manifold monosaccharides). Biochemically, carbohydrates are polyhydroxy aldehydes or ketones. Based on the chemical structure, the number of monosaccharides, and length, glycans are divided into monosaccharides, disaccharides, oligosaccharides, and polysaccharides. While monosaccharides consist of a single sugar molecule (*e.g.*, glucose, fructose, and galactose), the disaccharides consist of two monosaccharides (*e.g.*, maltose: glucose + glucose; sucrose: glucose + fructose; lactose: glucose+galactose, *etc.*) joined *via* glycosidic linkage(s) (Fig. 1). Carbohydrates that consist of three to ten monosaccharides are called oligosaccharides (*e.g.*, raffinose consists of trisaccharide) and those containing more than ten monosaccharides are called polysaccharides (*e.g.*, starch in plant cells and glycogen in animal cells). Dietary carbohydrates are the main sources of fuel (one gm of carbohydrate is equivalent to 4 calories) in most living organisms.

Carbohydrates or glycans are also involved in cellular protection, stabilization, organization, and barrier functions. At present, glycobiology is a swiftly emerging domain of biology, exhibiting relevance for biotechnology, and biomedicine, as well as basic research of carbohydrates, about physiological and various pathophysiological conditions (*e.g.*, host-pathogen interactions and subsequent adhesion, invasion, virulence, and pathogenicity of microorganisms). In the cellular system, carbohydrates exist in pure and conjugated form, with other molecules such as proteins and lipids. Following the synthesis of proteins *via* translation, several post-translational modifications are known to prevail. One of these modifications involves the addition of carbohydrates to the protein, at a specific pre-determined position using multiple enzymes. This process of carbohydrate-to-protein addition is called glycosylation. The glycosylated proteins are called glycoproteins. Not only proteins but some lipids and proteoglycans are also glycosylated. In general, the process of glycosylation occurs in specific cell organelles such as the endoplasmic reticulum (ER) and Golgi apparatus. Glycosyl transferases and glycosidases are the two enzyme groups involved in glycosylation. During glycosylation, the hemiacetyl group of a glycosyl donor reacts with the  $-OH$  or  $-NH_2$  group of the protein (glycosyl

accepter) forming a covalent bond. Glycoproteins are found in almost all living organisms including eubacteria, archaea, and eukaryotes. All eukaryotic living creatures from single-cellular to complex multicellular, generate glycoproteins. In most organelles of eukaryotic cells, proteins prevail as glycoproteins and are, therefore, involved in glycosylation.



**Fig. (1).** Structural distinctions of some eminent mono (a-c), di (d-f), and trisaccharide (f). Typical features comprise similar or dissimilar monosaccharides as linking units to confer a functional diversity to the respective di, oligo, and polysaccharides.

Multiple kinds of glycosylation are known to happen within a cell, such as *N*-linked glycosylation, *O*-linked glycosylation, *C*-linked glycosylation, glypiation, and phosphoglycosylation. The *N*-linked glycosylation takes place in the ER lumen. In this mode of glycosylation, glycans bind to the  $-\text{NH}_2$  group of the amino acid asparagine. On the other hand, in *O*-linked glycosylation, monosaccharides bind to the  $-\text{OH}$  group of the amino acids- serine, threonine, tyrosine, hydroxylysine, hydroxyproline side chains, or oxygens on lipids such as ceramide within the ER, Golgi apparatus, cytosol, and nucleus. To complete the glycosylation process, *N*-linked glycosylation entails the association of a special

## Vital Functions of Glycans in the Biological Systems

Ruma Rani<sup>1</sup>, Parth Malik<sup>2,3</sup>, Raj Singh<sup>4</sup>, Raman Kumar<sup>4</sup>, Vishal Haribhai Patel<sup>5</sup> and Tapan Kumar Mukherjee<sup>6,\*</sup>

<sup>1</sup> ICAR-National Research Centre on Equines, Hisar-125001, Haryana, India

<sup>2</sup> School of Chemical Sciences, Central University of Gujarat, Gandhinagar, Gujarat-382030, India

<sup>3</sup> Swarnim Startup & Innovation University, Bhoyan-Rathod, Gandhinagar-Gujarat, India

<sup>4</sup> Department of Biotechnology, Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala, Haryana 133207, India

<sup>5</sup> Institute of Biotechnology, Amity University, Noida-201301, Uttar Pradesh, India

<sup>6</sup> Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India

**Abstract:** Glycans and their various conjugates namely glycoproteins, glycolipids, and proteoglycans not only coat all the cells in nature and interact with the extracellular matrix (ECM) molecules but are also located in the intracellular regions of every living organism. Glycans mediate or modulate numerous biological roles that are essential for life. This most abundant cellular molecule is necessary to maintain various general and specialized functions of the cells. Some of the major vital roles of glycans include maintenance of the structural integrity and protection of the cells, cell adhesion, cell-t-cell communication, crosstalk, and bidirectional cell signaling (both inside out and outside in). Briefly, this chapter predominantly focuses on the role of glycans and their various conjugates in maintaining the structural integrity of biological membranes and the overall cells, the different modulatory functions of glycans, and their implication in nutrient sequestration. Additionally, a brief outline of the role of glycans on intrinsic or intra-species recognition and extrinsic or interspecies recognition is discussed. Overall, the biological importance of glycans and their conjugates is elaborated.

**Keywords:** Extrinsic/Inter-species recognition of Glycans, Glycans, Glycoproteins, Glycolipids, Intra-species/intrinsic recognition of Glycans, Proteoglycans, Structural/Modulatory role of Glycans.

\* Corresponding author Tapan Kumar Mukherjee: Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India; E-mail: tapan400@gmail.com

## INTRODUCTION

Glycans (carbohydrates: monosaccharides, disaccharides, oligosaccharides, and polysaccharides) are widely distributed and abundantly present in every cell of a living organism including all compartments and organelles, extracellular spaces (the extracellular matrix, glycocalyx) and even in the body fluids such as animal cell's blood. Thus, glycans are recognized as one of the most important building blocks of the living system. Different organisms are equipped to make unique complements of glycan structures by themselves, using dissimilar and sometimes, unusual monosaccharides. Enzymatic addition of glycans to other biological molecules such as proteins (*e.g.* glycoproteins, proteoglycans) and lipids (glycolipids) is famously recognized as glycosylation. The process of glycosylation happens in a cell and tissue-specific manner. In eukaryotes, the intracellular organelles namely endoplasmic reticulum (ER) and Golgi apparatus control the process of glycosylation at multiple levels. Unlike genome, exome, and proteome, it works in a non-template manner. Free glycans and various glycan conjugates including glycoproteins, glycolipids, and proteoglycans are involved in a vast array of biological functions.

The complexity and heterogeneity of glycan structures have impaired the rapid progress of glycoscience, delaying the understanding of the various roles of glycans in nature. However, in the last two or three decades, discoveries of a series of genetic and biochemical analysis tools and techniques have broadened the knowledge of the biological roles of glycans. Significant developments in nuclease-based gene editing, proteomics, and quantitative transcriptomics are now utilized to investigate protein glycosylation by identifying and focusing on glycosylation-related enzymes. Newly developed *in silico* models forecast different cell's capacity for glycosylation. The accurate and refined mapping of glycosylation pathways makes it easier to use genetic methods to address the various activities of the large glycoproteome. These strategies make use of widely accessible cell biology tools, and it is believed that the most notable developments towards a more comprehensive integration of glycosylation in general cell biology will come from the application of (single cell) transcriptomics, genetic screens, genetic engineering of cellular glycosylation capacities, and custom glycoprotein therapeutic design.

Today, it is well known that the biological functions of glycans vary from relatively subtle to crucial for the growth and development of the embryo, maintenance, and survival of a living organism, commencing from the unicellular prokaryotes (microorganisms) to complex multicellular eukaryotes, such as humans. The inceptive studies focused on the structural and modulatory roles of glycans under various physiological and pathophysiological conditions including

intracellular folding and stability of proteins and lipids and the ability to interfere with carbohydrate-protein, carbohydrate-carbohydrate, and glycoprotein-glycoprotein interactions that affect the proliferation, differentiation, migration and even invasion of cancer cells. However, glycans and their conjugates prevail widely in the periphery of the plasma membrane and glycocalyx. Of note, glycocalyx is defined as a cell surrounded by dense, gel-like meshwork, and constitutes a physical barrier for any material to enter a cell. The cell surroundings or peripheral glycans are critical mediators of cell adhesion, cell-to-cell communication, and various cell signaling mechanisms. These actions of glycans are necessary for the survival and maintenance of living organisms. In the subject of cell communications, glycans, and their conjugates are intricately related to the “inside-out” and “outside-in” bidirectional signaling of a cellular system. Additionally, secretory glycoproteins are involved in various biological functions of a living body. Several studies are now dedicated to understanding the role of glycans and their conjugates on the host (*e.g.* immunological cells)-pathogen (viruses, bacteria *etc.*) interactions, and the subsequent attachment, entry, and pathogenicity. In contrast, the recognition of pathogens by the immunological cells and molecules helps to eliminate these pathogens, and glycans take significant roles in these actions. Thus, glycans are part of an elaborate communication system vital for cellular recognition, cell-cell interactions, protein transport, immune defense, and more.

The biological functions of glycans are categorized into two prominent domains, relying on their (i) structure-modulatory traits, and (ii) explicit identification by erstwhile molecules, majorly glycan-binding proteins (GBPs). Of note, the GBP actions could be intrinsic (facilitating glycans from the same organism) or extrinsic (recognizing glycans from a different organism). The intrinsic GBPs are capable of recognizing glycans on the same cell and assist in cell-cell interactions (majorly responding to extracellular molecules). Contrary to this, the extrinsic GBPs exhaustively comprise pathogenic microbial adhesions, agglutinins, or toxins though some of these roles maintain a symbiotic association. Fig. (1) depicts the explicit functions of glycans molecular aspects, and their mutual correlations, manifesting for their explicit recognition. Additionally, a broad classification of glycans is highlighted, demonstrating the roles of intrinsic and extrinsic GBPs in the screening of glycans.

This chapter predominantly focuses on the role of glycans and their various conjugates in structural-modulatory functions and nutrient sequestration. Additionally, a very brief outline of the role of glycans on intrinsic or intraspecies recognition and extrinsic or interspecies recognition is discussed. The structural and modulatory roles of glycans section briefly describe their functions in maintaining the structural integrity of the biological membranes, the involvement

## Understanding Congenital Glycosylation Disorders

Himel Mondal<sup>1</sup>, Shaikat Mondal<sup>2</sup> and Rajeev K. Singla<sup>3,\*</sup>

<sup>1</sup> Department of Physiology, All India Institute of Medical Sciences, Deoghar, Jharkhand-814152, India

<sup>2</sup> Department of Physiology, Raiganj Government Medical College and Hospital, Raiganj, West Bengal, India

<sup>3</sup> Joint Laboratory of Artificial Intelligence for Critical Care Medicine, Department of Critical Care Medicine and Institutes for Systems Genetics, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu, China

**Abstract:** Congenital Disorders of Glycosylation (CDG) encompass a rare and complex group of genetic diseases characterized by abnormalities in the fundamental process of glycosylation. There is an abnormal synthesis or attachment of the glycan moiety of glycoproteins and glycolipids. CDG arises from mutations in genes responsible for various steps in glycosylation within the endoplasmic reticulum and Golgi apparatus. These mutations disrupt the synthesis and transfer of sugar moieties, resulting in the production of defective glycoproteins and glycolipids. Common symptoms of the disease include developmental delays, intellectual disabilities, hypotonia, seizures, and organ dysfunction. The array of CDG subtypes stems from the multitude of underlying genetic mutations and disturbed glycosylation processes making the diagnosis and management challenging. Diagnosis of CDG relies on a multifaceted approach. Clinical evaluation, biochemical analysis, and genetic testing are all essential components. The advent of next-generation sequencing has significantly improved our ability to identify the specific gene mutations responsible for individual CDG subtypes. The management of CDG involves primarily symptom alleviation and enhancing the quality of life. A multidisciplinary approach is fundamental, encompassing supportive care, physical and speech therapies, and medications targeting specific complications.

**Keywords:** Glycosylation, Glycosaminoglycans, Intellectual disability, Lipids, Mutation, Muscle hypotonia, Muscle weakness.

### INTRODUCTION

In the intricate landscape of human genetics and cellular biology, there exists a group of conditions known as Congenital Disorders of Glycosylation (CDG).

\* Corresponding author Rajeev K. Singla: Joint Laboratory of Artificial Intelligence for Critical Care Medicine, Department of Critical Care Medicine and Institutes for Systems Genetics, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu, China; E-mail: rajeevsingla26@gmail.com

These disorders represent a unique and complex realm of genetic diseases, where the very building blocks of life - sugars - play a pivotal role. CDGs are a diverse group of disorders, each with its own genetic basis and clinical manifestations, yet they all share a common thread: disruptions in glycosylation processes within our cells.

Glycosylation is a fundamental cellular process involving the attachment of sugar molecules to proteins and lipids, transforming them into glycoproteins and glycolipids. This seemingly simple addition of sugars, however, underpins a myriad of crucial functions within the human body. Glycosylation is involved in protein folding, stability, and function, cellular signaling, and the proper functioning of various organs and tissues. When this process goes awry, as it does in CDG, the consequences can be profound [1].

The journey into the world of CDG begins with a deeper understanding of its genetic origins. Genetic mutations disrupt the glycosylation pathways within cells, resulting in a wide range of clinical presentations. From developmental delays to intellectual disabilities, seizures to hypotonia, the symptoms of CDG are as diverse as the genetic mutations underlying them. This clinical diversity poses a substantial diagnostic challenge, often requiring advanced genetic testing to pinpoint the exact mutations responsible for each individual's condition [2].

This chapter aims to discuss the intricacies of CDG, offering insight into its causes, the signs and symptoms it presents, the diagnostic hurdles faced by both patients and clinicians, and the ongoing efforts to develop effective treatments. This would explore defects in protein *N*-glycosylation, disorders of protein *O*-glycosylation, glycosaminoglycan (GAG) synthesis defects, lipid and GPI-anchor glycosylation defects, and multifaceted pathways that interconnect in the complex network of glycosylation processes.

The discovery and understanding of CDG are a relatively recent development in the field of medical genetics. Here is a brief history of CDG discovery and our evolving understanding of these complex disorders. The origins of CDG can be traced back to the late 20th century when clinicians and researchers began to observe a group of patients with unexplained, multi-systemic symptoms that did not fit into any known diagnostic categories. These symptoms included developmental delays, intellectual disabilities, and various organ dysfunctions. The first recognized case of CDG was reported in the 1980s. Professor Jaak Jaeken reported neurological disorders in twin girls. In the late 1980s and early 1990s, researchers began to characterize the underlying genetic and biochemical defects in CDG patients. They identified mutations in specific genes involved in glycosylation pathways as the root cause of these disorders. As research

progressed, it became evident that CDG was not a single disorder but a group of disorders with distinct genetic and clinical features. Researchers started identifying and classifying various CDG subtypes based on the specific glycosylation pathways affected. Advances in genetic testing, particularly the development of next-generation sequencing technologies, greatly facilitated the diagnosis of CDG. This allowed for more accurate and efficient identification of the genetic mutations responsible for individual cases. As awareness of CDG grew within the medical community, more cases were diagnosed and reported [3]. Ongoing research into CDG has led to a deeper understanding of the molecular mechanisms involved in glycosylation and the consequences of glycosylation defects. This knowledge has spurred efforts to develop potential therapies and interventions for CDG. Today, CDG research continues to advance, offering hope for improved diagnostic techniques and therapeutic interventions. While there is no cure for CDG at present, ongoing studies aim to enhance the quality of life for individuals living with these rare disorders.

In summary, the discovery and understanding of CDG have evolved significantly over the past few decades. What once seemed like a mysterious and unexplained group of disorders is now being dissected at the genetic and molecular levels, with ongoing efforts to provide better diagnosis, management, and treatment options for affected individuals and their families.

## **CAUSES OF CONGENITAL DISORDER OF GLYCOSYLATION**

CDGs are a group of rare genetic disorders caused by mutations in genes that encode enzymes or transporters involved in the glycosylation process. Glycosylation is a complex biological process where sugar molecules (glycans) are attached to proteins (glycoproteins) and lipids (glycolipids). When this process is disrupted due to genetic mutations, it can result in various CDG subtypes, each with distinct clinical manifestations. Here are some key causes and factors contributing to CDGs. The disorder can be broadly classified into four groups - protein N-glycosylation, protein O-glycosylation, lipid glycosylation, and other glycosylation pathways and multiple glycosylation pathways [4].

### **Protein N-Glycosylation**

This is one of the most well-studied glycosylation pathways and involves the attachment of complex sugar chains (glycans) to specific asparagine (N) residues of proteins. CDGs associated with protein N-glycosylation primarily result from defects in the synthesis, assembly, or transfer of N-linked glycans. These disorders can manifest with a wide range of symptoms, including developmental delays, intellectual disabilities, seizures, and various organ dysfunctions. Classic

## The Biology of Advanced Glycation End Products

Parth Malik<sup>1,2,†</sup>, Ruma Rani<sup>3,†</sup> and Tapan Kumar Mukherjee<sup>4,\*</sup>

<sup>1</sup> School of Chemical Sciences, Central University of Gujarat, Gandhinagar, Gujarat-382030, India

<sup>2</sup> Swarnnim Startup & Innovation University, Bhoyan-Rathod, Gandhinagar-Gujarat, India

<sup>3</sup> ICAR-National Research Centre on Equines, Hisar-125001, Haryana, India

<sup>4</sup> Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India

**Abstract:** This chapter is dedicated to the biology of advanced glycation end products (AGEs). In 1912, AGEs were first identified by French chemist Louis-Camille Maillard. Early investigation revealed AGE generation during food preparation (cooking) at high temperatures, wherein carbohydrates (*e.g.* glucose/glycan) slowly react with various proteins *via* concomitant generation of Schiff's base and Amadori products. This non-enzymatic process of AGE generation is termed glycation. Later, subsequent investigations revealed that AGE is exogenously produced during cooking and other processing of foods and also endogenously generated in the human body including blood, skin, and other tissues. To date, more than 20 AGEs are postulated to prevail within human blood, tissues, and food resources. AGEs are optical sensitive molecules and based on their optical sensitivity AGEs are distinguished into fluorescent and non-fluorescent categories. The most important non-fluorescent components are carboxymethyl-lysine (CML), carboxyethyl-lysine (CEL), and pyrrolidine while pentosidine and methylglyoxal-lysine dimer (MOLD) are prominent compounds having fluorescent sensitivity. AGE binds with several receptor molecules, the prominent among which are receptors for advanced glycation end products (RAGE). Additional cell surface molecules capable of binding with AGE including macrophage scavenger receptors (MSRs) type A, B1 (CD36), oligosaccharyltransferase-48/OST48, also termed "AGE receptor 1" (AGE-R1), 80K-H phosphoprotein (AGE receptor 2, AGE-R2), and galectin-3 (AGE receptor 3, AGE-R3), the scavenger receptor family (SR-A, SR-B, SR-1, SR-E, LOX-1, FEEL-1, FEEL-2, and CD36). This chapter describes the steps of AGE synthesis, their biochemical characterization, and the implication of the AGE-RAGE interactions at the cellular platform.

\* **Corresponding author Tapan Kumar Mukherjee:** Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India; E-mail: tapan400@gmail.com

† These authors contributed equally to this work.

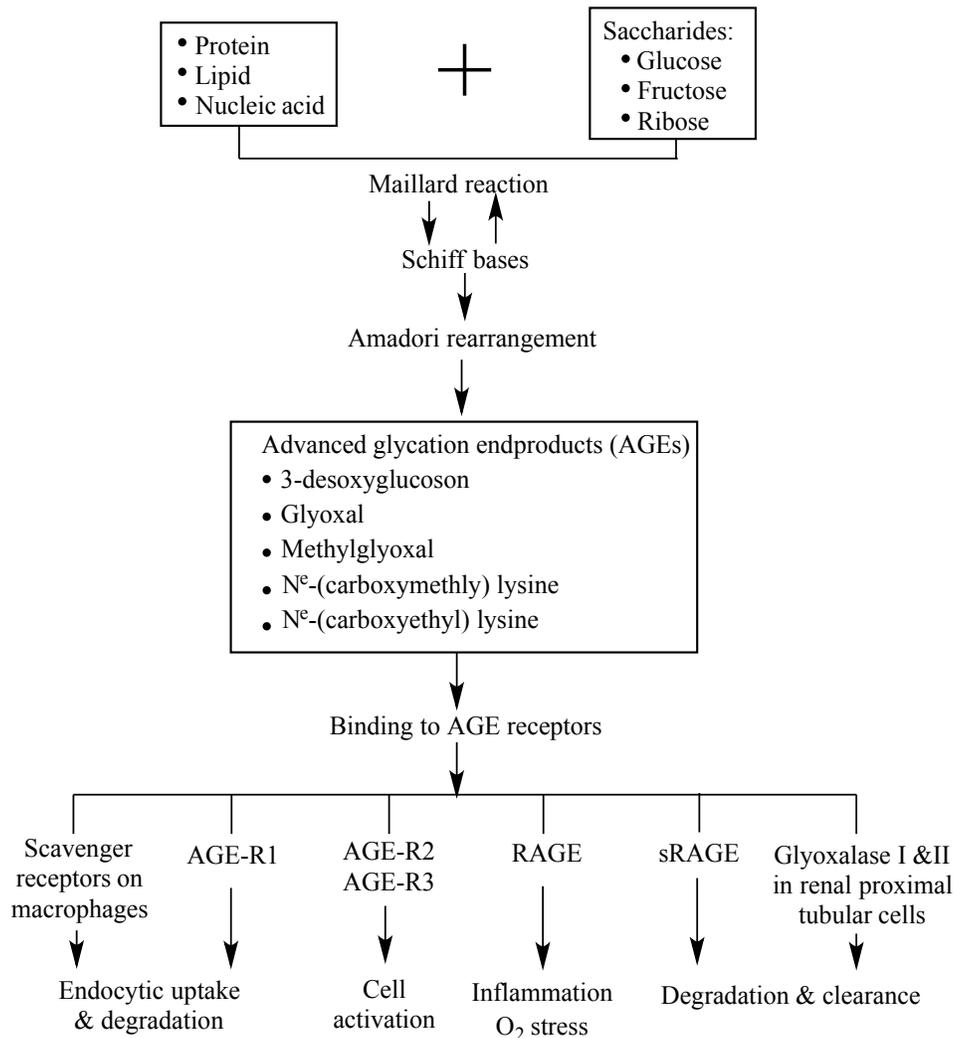
**Keywords:** Advanced glycation end products (AGE), Glycation, Lipid peroxidation, Methylglyoxal, Oxidative and Inflammatory stress, Reactive oxygen species (ROS), Skin autofluorescence.

## INTRODUCTION

The process of glycation was initially introduced in 1912 by French chemist Louis-Camille Maillard and is therefore also recognized as the “Maillard reaction”. In the typical process, free reducing sugars spontaneously (without the involvement of any enzymes/ catalysts) gradually react with free amino groups ( $-NH_2$ ) of proteins, DNA, and lipids, culminating in the formation of Amadori products. The Amadori products undergo diverse, irreversible dehydration and rearrangement reactions and generate “advanced glycation end products (AGEs)”. The biochemical analysis of AGE formation indicates that the typical process of glycation commences *via* sugar carbonyl or aldehyde group and the amino acid nucleophilic, free  $-NH_2$  group chemical reaction, swiftly generating Schiff base as an unstable adduct. The spontaneous rearrangements of this adduct reversibly form “Amadori product” as a further stable fraction. Finally, the intermediate Amadori products undergo irreversible oxidation, dehydration, polymerization, and cross-linking to form AGEs (Fig. 1) [1]. The depicted AGE molecules in Fig. (1) are 3-deoxyglucosone, glyoxal, methylglyoxal, N<sup>ε</sup>-(carboxymethyl) lysine, and N<sup>ε</sup>-(carboxyethyl) lysine, formed as a consequence of Amadori rearrangement of the Schiff bases from the Maillard reaction.

AGE generation is mediated endogenously *i.e.* within the human body and exogenously (outside the human body). The most significant exogenous generation of AGEs is from food. *Grossin and associates* elaborately discussed the significance of dietary AGEs and their interaction with RAGE amidst aging [2]. During the processing or cooking of food on an industrial or domestic level, the Maillard reaction is frequently employed for improving the color, flavor, aroma, and consistency of foods. However, a considerable extent of AGE generation happens during sugar-protein simultaneous processing *via* cooking [3]. AGE is also produced inside the human body such as in blood, skin, and other tissues. There is a substantial possibility for the glycation of cellular proteins compared to the plasma proteins. Several studies demonstrate a familiar, intracellular generation of dicarbonyls *via* triose phosphate fragmentation and lipid peroxidation (Fig. 2). The event of glycation culminates in lost protein function and deteriorating tissue elasticity, including those of blood vessels, skin, and tendons. All major classes of biomolecules such as DNA, proteins, and phospholipids are affected by glycation. The estimated damage level indicates that 0.1-1% of lysine and arginine fractions on proteins, 1 in  $10^7$  DNA nucleotides, and 0.1% alkaline phospholipids are affected by glycation [4].

In human tissues and blood, the glycation reaction is highly aggravated particularly in case of hyperglycemia and enhanced tissue oxidative stress [5]. As a result, glycation eventually mediates the pathogenesis of diabetic vascular troubles apart from cellular and tissue aging [6]. No enzymatic process is presently known to eliminate AGEs from the human system, including cells, tissues, and blood. Nevertheless, some studies claimed that AGEs are catabolized in renal proximal tubular cells. Thus, the glycation process is in agreement with the belief that metabolic waste accumulation promotes aging.



**Fig. (1).** Advanced-glycation end-product (AGE) formation by Maillard reaction and the fates after binding with different AGE receptors. AGE-R1, R2, and R3: AGE receptors R1, R2, and R3; RAGE: receptor for AGE; sRAGE: soluble-form RAGE.

## Receptor for Advanced Glycation End Products in Health and Physiology

Ruma Rani<sup>1,†</sup>, Parth Malik<sup>2,3,†</sup> and Tapan Kumar Mukherjee<sup>4,\*</sup>

<sup>1</sup> ICAR-National Research Centre on Equines, Hisar-125001, Haryana, India

<sup>2</sup> School of Chemical Sciences, Central University of Gujarat, Gandhinagar, Gujarat-382030, India

<sup>3</sup> Swarnim Startup & Innovation University, Bhoyan-Rathod, Gandhinagar-Gujarat, India

<sup>4</sup> Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India

**Abstract:** The transmembrane protein receptor for advanced glycation end products (mRAGEs) is recognized as an immunoglobulin class of molecule. Mammalian cells produce a carboxy terminus truncated version of RAGE, either as endogenous soluble RAGE (esRAGE) or soluble RAGE (sRAGE), both being generated *via* proteolytic cleavage or alternative mRAGE-mRNA splicing. Through its extracellular domains (V, C1, and C2), RAGE interacts with seemingly unrelated ligands such as advanced glycation end products (AGEs), high mobility group box protein 1 (HMGB1), S100/calgranulin family, lysophosphatidic acid (LPA), oligomeric forms of amyloid beta peptide (A $\beta$ -peptide), islet amyloid polypeptide (IAPP), attributing to the recognition as multi-ligand receptor. Under physiological conditions, lung tissues exhibit abundant RAGE expression compared to others, being involved in the development, spread, and homeostatic regulation, the prominent of which are lung alveolar type 1 (AT-1) epithelial cells. However, in pathophysiological conditions, supraphysiological expression of RAGE and its ligands and subsequent receptor-ligand interactions result in the aggravation of oxidative stress and inflammation, causing the propagation of various non-communicable disease conditions. The physiological RAGE expression may protect against non-small cell lung cancers (NSCLCs), as suppressed RAGE expression in lung tissues may complicate NSCLCs. The protective role of RAGE in lung tissues is surprisingly contrary to its activities in other cancers, which are unanimously characterized by its enhanced expression-driven propagation of the conditions. Anti-RAGE molecules including esRAGE/sRAGE attenuate RAGE-dependent multiple diseased conditions.

\* Corresponding author Tapan Kumar Mukherjee: Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India; E-mail: tapan400@gmail.com

† These authors contributed equally to this work.

**Keywords:** Endogenous soluble RAGE (esRAGE), Inflammation, Multiligand Receptor, Oxidative stress, Pathophysiological conditions, RAGE, RAGE ligands, Receptor for advanced glycation end products (RAGE), Soluble RAGE (sRAGE).

## INTRODUCTION

The year 1992 witnessed the first ever experimental evidence for receptors for advanced glycation end products *i.e.* RAGE expression in the bovine pulmonary tissues, creditable to the significant efforts of *Schmidt and associates* [1]. The gene for the RAGE molecule is located at chromosome 6, exhibiting 11 exons and 10 introns, prevailing as highly polymorphic with several alternative forms or splice variants being reported. RAGE protein is recognized as a transmembrane immunoglobulin (Ig) class of molecule, concomitantly functioning as a primitive pattern recognition receptor (PPR) molecule. Structurally, this single-spanning transmembrane protein consists of an extracellular portion having V, C1, and C2 domains. The RAGE is recognized as a “multi-ligand receptor”, and interacts with these seemingly unrelated ligands, including advanced glycation end products (AGEs), high mobility group box protein 1 (HMGB1), S100/calgranulin family, lysophosphatidic acid (LPA), oligomeric amyloid beta peptide (A $\beta$ -peptide), and islet amyloid polypeptide (IAPP).

In addition to membrane-bound RAGE (mRAGE), C-(carboxy) terminus truncated RAGE commonly prevails in bodily fluids, including bronchoalveolar lavage (BAL), the fluid surrounding lungs. Soluble RAGE (sRAGE, 50 kDa) or endogenous soluble RAGE (esRAGE, 46 kDa) are the two names given to the circulating RAGE. Although esRAGE is produced by alternative splicing of the RAGE (AGER) gene [2], sRAGE is produced by proteolytic cleavage of the receptor's extracellular domain [3, 4]. Notably, membrane-bound RAGE may use sRAGE/esRAGE as a decoy receptor.

Under completely normal physiological conditions in comparison to all other tissues of the mammalian body, RAGE is most abundantly expressed in the pulmonary tissues [5]. The basolateral membrane of pulmonary alveolar type 1 (AT-1) epithelial cells is the exclusive RAGE expression site in the lungs. RAGE may have a physiological role in lung development [6, 7]. In a significant effort on animal model experiments, *Wolf and colleagues* used RAGE knock-out mice and established that RAGE regulates the differentiation of alveolar epithelial cells, modulating the development and maintenance of lung tissue structure-function [8]. In pathophysiological conditions, supraphysiological expression and subsequent interaction of RAGE with its various ligands, such as AGE and HMGB1, lead to enhanced inflammatory and oxidative stress, eventually manifesting as multiple diseased conditions. Several lines of evidence also

decipher functional similarities of the RAGE molecule with adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). VCAM-1 and ICAM-1 are cell surface immunoglobulin class of molecules and are involved in pro-inflammatory and pro-oxidative reactions. Thus, RAGE is implicated in the propagation of multiple diseases *via* enhanced inflammatory and oxidative stress. A comprehensive literature survey revealed RAGE involvement in the complication of various pulmonary diseases including asthma, chronic bronchitis (CB), cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), acute lung injury (ALI), acute respiratory distress syndrome (ARDS) and pulmonary arterial hypertension [9, 10]. The major non-pulmonary diseases complicated by RAGE are vascular complications associated with diabetes and atherosclerosis, neurological vascular complications (*e.g.* Alzheimer's disease, AD), and various cancers including breast, ovarian, endometrial, pancreatic, colon, *etc.* However, several lines of evidence indicated that an increased level of RAGE protects against non-small cell lung cancers (NSCLCs). Of note, ~85% of lung cancers are of NSCLC regime. This chapter describes the RAGE signaling mediated through its various ligands, the structure-functional relationships of RAGE, and its ligands alongside the physiological and pathophysiological roles.

### **CHARACTERIZATION OF RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS GENE**

- The RAGE gene lies on chromosome 6 (6p21.3), typically comprising 11 exons interlaced with 10 introns [11].
- The pre-B-cell leukemia transcription factor 2 (PBX2) homeobox gene and a notch homolog, located close to the human leukocyte antigen (HLA) locus are also present in proximity to the RAGE gene along with its 11 exons and 10 introns [12].
- The highly polymorphic nature of the RAGE gene has been well-characterized thus far with several alternative splice variants.
- Although the group identifies 15 transcripts with RAGE variants [13], some other research lists as many as 19 transcripts [2, 14].
- The predominant transcript, NM\_001136, with 11 exons, 404 amino acids (aa), and a molecular weight of 55 kDa (cDNA: 1492 bp, DNA sequence: 4557 bp), is identified amongst the four major transcript variants for RAGE [2]. The longest isoform (NM\_001206929), codes for a protein with 420 aa and has 11 exons. (Fig. 1).
- N-terminus truncated RAGE (N-RAGE) is the subsequent transcript, having an initiation codon at exon 3 and an in-frame stop codon in the intron sequence. It encodes for 42 kDa short protein containing only 303 aa and no V-type immunoglobulin domain. This isoform can transport and localize into the

## Receptor for Advanced Glycation End Products as a Mediator of Inflammation and Oxidative Stress

Ruma Rani<sup>1,†</sup>, Parth Malik<sup>2,3,†</sup> and Tapan Kumar Mukherjee<sup>4,\*</sup>

<sup>1</sup> IICAR-National Research Centre on Equines, Hisar-125001, Haryana, India

<sup>2</sup> School of Chemical Sciences, Central University of Gujarat, Gandhinagar, Gujarat-382030, India

<sup>3</sup> Swarnim Startup & Innovation University, Bhoyan-Rathod, Gandhinagar-Gujarat, India

<sup>4</sup> Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India

**Abstract:** The receptor for advanced glycation end products (RAGEs) is a cell surface immunoglobulin class of molecules. RAGE prevails as a multiligand receptor capable of interacting with various ligands, the prominent amongst which is “advanced glycation end products (AGE)”. The ligand-RAGE axis leads to an aggravated extent of inflammation and oxidative stress, activating various pro-inflammatory and pro-oxidative transcription factors such as nuclear factor kappa B (NF-κB). The binding of NF-κB to the promoter region of the RAGE gene activates its transcription. Once expressed, RAGE interacts further with its multiple ligands including AGE, HMGB1, S100, *etc.*, culminating in aggravated inflammatory and oxidative stress. Thus, RAGE which is a product of an increased level of inflammation and oxidative stress, once produced perpetuates a brutal cycle of self-propagation through sustained interaction with various ligands and subsequent inflammation and oxidation stress. Several levels of crosstalk possibilities prevail between pro-inflammatory and prooxidative reactive molecules. Sustaining a high level of pro-inflammatory and prooxidative reactions is the basic requirement to complicate various non-communicable disease conditions including diabetes-associated vascular complications, cardiovascular disorders (CVDs), pulmonary diseases, cancers, and others. This chapter describes the basic mechanism through which RAGE fuels the inflammatory and oxidative stress on a cellular front.

**Keywords:** Advanced Glycation End products (AGE), Inflammation, Oxidative Stress, Proinflammatory and Prooxidative Transcription Factors (NF-κB and SP1), Reactive Oxygen Species (ROS), Receptor for Advanced Glycation End Products (RAGE).

\* Corresponding author Tapan Kumar Mukherjee: Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India; E-mail: tapan400@gmail.com

† These authors contributed equally to this work.

## INTRODUCTION

RAGE resides as a single-spanning transmembrane receptor protein belonging to the immunoglobulin class of proteins. The molecule RAGE is now, well-perceived as a pattern-recognition receptor (PRR) of the innate immune system. Being a multiligand receptor, RAGE interaction with various ligands confers a substantial significance to the three-dimensional RAGE structural configuration rather than its specific amino acid sequence. The well-characterized ligand molecules that can interact with the RAGE molecule are advanced glycated end products (AGE), S100, high mobility group box protein 1 (HMGB1, also known as amphoterin), amyloid  $\beta$ -peptide, and others [1, 2]. AGE is by far the, most well-characterized RAGE ligand. The substantial diversity of RAGE ligands could be described by exploring a common functional link for all ligands, such as persistent anionic surfaces, complementary to excessively alkaline and electropositive topography of RAGE ligand-binding domains. Such a sturdy electrostatic interaction induces the formation of a tight receptor-ligand complex, culminating in prolonged stimulation of downstream signaling pathways [3].

Initial studies by *Schmidt* and *associates* illustrated that the RAGE interaction with manifold ligands disseminates and propagates inflammatory conditions. While controlled, low inflammation (acute) is a homeostatic mechanism that eliminates infectious pathogens and mends damaged, stressed cells and tissues, excessive inflammation (chronic) is detrimental to the human body. Chronic inflammation complicates various non-communicable disease conditions in the human body. The involvement of RAGE in inflammatory stress has been confirmed by manifold experimental evidence. First, RAGE is aggravatedly expressed in all inflammatory lesions, including lung disorders [*e.g.* asthma, chronic obstructive pulmonary diseases (COPD), acute lung injury (ALI), acute respiratory disease syndrome (ARDS), cystic fibrosis (CF), chronic bronchitis (CB), sepsis and pulmonary hypertension, diabetes-associated vascular complications, cardiovascular complications (CVDs), specifically atherosclerosis, rheumatoid arthritis (RA), inflammatory kidney disease (glomerulonephritis), inflammatory bowel disease (IBD), various kinds of cancers (such as breast, ovary, pancreas, colon/ colorectal) and others [4 - 6]. Second, the RAGE promoter (the RNA polymerase binding site of the RAGE gene) houses the binding sequence of various pro-inflammatory and prooxidative transcription factors such as nuclear factor kappa B (NF- $\kappa$ B) and specificity protein 1 (SP1). Ligands-RAGE interaction activates these pro-inflammatory and pro-oxidative transcription factors. The third soluble RAGE (sRAGE), a condensed structure of the receptor spanning the extracellular ligand-binding domain (that subsequently competes with cell membrane-anchored RAGE for ligand binding), reduced inflammatory outcomes in all models screened to date, including delayed-type

hypersensitivity (DTH), colitis and periodontitis. Studies using F(ab)<sub>2</sub> fragments mediated hindered ligand-RAGE binding complemented such observations, in particular for the highest concentration. Fourth, RAGE not only activates various adhesion molecules (e.g. vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), but a few studies also recognized RAGE as an integrin molecule, capable of bi-directional signaling (inside out and outside in). Of note, adhesion molecules are recognized as a cell-surface immunoglobulin class of molecules [7]. In addition to aggravating inflammation, RAGE also instigates the production of reactive oxygen species (ROS) and consequent oxidative stress, on a cellular front. Superoxide (O<sub>2</sub><sup>•-</sup>), hydroxyl (OH<sup>•</sup>) and relatively less reactive hydrogen peroxides (H<sub>2</sub>O<sub>2</sub>) are the major cellular level ROS [8, 9].

In normal physiological conditions, the human cell cytoplasm maintains a robust mechanism to control the redox status of the cells. Of note, a reduced environment is hereby maintained *via a* pH of 7.2. This reducing environment of human cell cytoplasm is regulated by several endogenous antioxidants, like reduced glutathione (GSH) and thioredoxin. The *in vivo* cellular system produces vitamins C and E as exogenous food-derived antioxidants along with multiple enzymatic antioxidants such as peroxidases (e.g. glutathione peroxidase) and superoxide dismutase (SODs) [10]. Under normal physiological conditions, ROS is predominantly generated by mitochondria *via* carrier-mediated electron transfer such as flavin adenine dinucleotide (FAD), Nicotinamide Adenine Dinucleotide (NAD), coenzyme Q, and cytochrome C. Of note, the electron carriers are transferred from complex I to complex IV, *via* complex III and complex II. During this electron transfer, 1-2% electron leaks (single electron reduction) from complex III and to some extent from complex I occur, leading to ROS generation. However, under pathophysiological conditions, the ROS generation from the mammalian cell mitochondria considerably enhances, culminating in oxidative stress. Additionally, under complete physiological conditions, ROS is formed by several cellular oxidoreductases, like NADPH oxidase, xanthine oxidase, *etc.* This low level of ROS acts as a secondary messenger and therefore does not cause any adverse cellular effects [11 - 13]. High levels of ROS generation lead to oxidative stress which complicates various diseased conditions. Several lines of evidence indicate that enhanced oxidative stress induces the RAGE expression. Once RAGE is expressed, the ROS generation is further enhanced *via* interacting with its multiple ligands such as AGE. Therefore, RAGE perpetuates a vicious self-generation cycle *via* aggravated ROS generation [8].

Further, several lines of evidence indicate that oxidative stress and inflammation are closely interlinked *via* multiple crosstalk regulations. Chronic inflammation and oxidative stress complicate various diseased conditions, making it a prominent

## Receptor for Advanced Glycation End Products in Pulmonary Diseases

Parth Malik<sup>1,2,†</sup>, Ruma Rani<sup>3,†</sup> and Tapan Kumar Mukherjee<sup>4,\*</sup>

<sup>1</sup> School of Chemical Sciences, Central University of Gujarat, Gandhinagar, Gujarat-382030, India

<sup>2</sup> Swarnnim Startup & Innovation University, Bhoyan-Rathod, Gandhinagar-Gujarat, India

<sup>3</sup> ICAR-National Research Centre on Equines, Hisar-125001, Haryana, India

<sup>4</sup> Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India

**Abstract:** The receptor for advanced glycation end products (RAGE) is characterized as a multi-ligand pattern recognition receptor molecule exhibiting physiologically profuse expression in the lung alveolar type 1 (AT-1) epithelial cell's basolateral region. Advanced glycation end products (AGEs) are the most prominent among the multiple ligands of RAGE in lung tissues. Other major RAGE ligands comprise high mobility group box protein 1 (HMGB-1) and S100/calgranulin. In various pathophysiological conditions, lung tissues express the supraphysiological level of RAGE and its multiple ligands. In physiological conditions, the interaction of RAGE with its ligands assists in the maturity, spreading, and maintenance-enabled homeostasis of lung epithelial cells. Thus, physiologically abundant expression of RAGE in the lung AT-1 cells maintains their morphology and specific architecture. In physiological conditions, high basal level expression of RAGE in the lung tissues guards against the development of non-small cell lung cancers (NSCLCs), wherein decreased RAGE extents are correlated with non-small cell lung cancer (NSCLC) complications. However, in the lung tissues under pathophysiological conditions, supraphysiological expression of RAGE and its various ligands stimulates inflammation and oxidative stress-related cell signaling molecules. This aggravated extent of inflammation and oxidative stress in the lung tissues leads to the propagation of manifold lung diseases namely, asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and cystic fibrosis (CF), acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), pneumonia, sepsis, bronchopulmonary dysplasia, and pulmonary hypertension. This chapter describes the physiological and pathophysiological role of RAGE in the lungs and the anti-RAGE therapy against various lung diseases.

\* **Corresponding author Tapan Kumar Mukherjee:** Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India; E-mail: tapan400@gmail.com

† These authors contributed equally to this work.

Tapan Kumar Mukherjee, Parth Malik & Ruma Rani (Eds.)  
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**Keywords:** Advanced glycation end products (AGE), Inflammatory stress, Lung diseases, Non-small cell lung cancers (NSCLCs), Oxidative stress, Receptor for advanced glycation end products (RAGE), RAGE-ligand interactions, RAGE inhibiting pharmacological agents.

## INTRODUCTION

The receptor for advanced glycation end products (RAGE) was first identified in the bovine lung endothelium as a target protein for advanced glycosylated end products (AGEs). RAGE prevails as a single-chain cell surface immunoglobulin (Ig) class of protein molecule and is thus recognized as a membrane-bound protein (mRAGE). RAGE is also available as a soluble RAGE (sRAGE) or endogenous soluble RAGE (esRAGE), generated *via* proteolytic cleavage or alternative mRNA splicing. In adult lung tissues, RAGE is highly expressed in alveolar type-1(AT-1) epithelial cells. Besides AT-1 cells, RAGE is also expressed in erstwhile lung cells, including endothelial and smooth muscle cells. The mRAGE is an extensively glycosylated, single-spanning transmembrane protein containing a ligand-binding extracellular structure [one V-type and two C-type domains], a transmembrane region, and a C-terminal cytosolic domain involved in signal transduction. Missing transmembrane and cytoplasmic domains is a noted feature of sRAGE although it does exhibit extracellular domains [1].

RAGE recognizes a substantial diverse group of ligands, including advanced glycation end products (AGEs), amyloid  $\beta$ -peptides, high mobility group box protein 1 (HMGB1), S100/calgranulin, advanced oxidation protein products (AOPPs), oxidized low-density lipoprotein receptor- 1 (Lox-1), fasciclin EGF-like, laminin-type EGF-like link domain-containing scavenger receptor-1/2 (FEEL1/2) and CD36. Thus, RAGE is considered a multi-ligand receptor molecule. The lung tissues expressed all major RAGE ligands, *viz.* AGEs, HMGB-1, and S100/calgranulin [2].

Conventional lung physiology is characterized by RAGE involvement in the adherence, spreading, and homeostasis maintenance of various cells including AT1 cells. RAGE is also involved in the overall homeostatic regulation of multiple lung functions. Evidence comes from the RAGE knockout (RAGE<sup>-/-</sup>) mice, which exhibited considerable aggravation in dynamic lung compliance with a suppressed maximal expiratory airflow [3, 4]. Nonetheless, high-level expression of RAGE or its ligands (exclusively, AGEs and HMGB1, S100, and subsequent aggravated RAGE-ligand interactions) leads to a complicated state of multiple lung diseases, *viz.* asthma, chronic bronchitis (CB), acute lung injury (ALI) and more severe regimes such as acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disorders (COPD), sepsis, cystic fibrosis

(CF), and idiopathic pulmonary fibrosis (IPF). The inevitable outcome of enhanced RAGE-ligand interactions is the aggravated extent of inflammatory and oxidative stress, leading to an aggravated state of various pulmonary diseases. Differentially altered immune responses are primarily caused by endogenous antigens, inhaled allergens, respiratory pathogens, and environmental pollutants. Airway mucosal surface-associated pattern recognition receptor (PRR) molecules identify these antigens as RAGE, and these antigens are ultimately eliminated by inducing immune responses. Since immunological cells such as monocytes, macrophages, neutrophils, and leukocytes secrete most of the RAGE ligands, these cells are essential for the initiation and propagation of RAGE-dependent inflammatory responses and oxidative stress. Inactivating RAGE or RAGE-ligand interaction may moderate the inflammatory and oxidative stress, thus easing the complications of various lung diseases. This chapter describes the physiological and pathophysiological aspects of RAGE in lung tissues [5, 6].

### **CELL-SPECIFIC EXPRESSION OF RAGE IN THE LUNG TISSUES**

The cell surface protein RAGE was first identified in bovine lungs. RAGE is most copiously expressed in the lung tissues compared to other tissues in the human body. *Neepor and colleagues* for the 1<sup>st</sup> time detected RAGE expression in the bovine lung tissues. Several subsequent investigations examined cell-explicit RAGE expression in the lungs. While initial studies by *Katsuoka and colleagues* localized RAGE in the pulmonary epithelial type 2(AT2) cells, studies of *Demling, Shirasawa, and Fehrenbach* groups demonstrated the exclusive RAGE expression on the alveolar type 1 (AT1) epithelial cells. Of note, these studies did not identify the RAGE expression in AT2 epithelial or capillary endothelial cells. *Fehrenbach and associates* used quantitative immunoelectron microscopy in rat and human lung specimens, establishing RAGE localization in the basal cell membrane of AT1 cells. *Shirasawa and colleagues* using an identical approach also identified RAGE expression on the AT1 epithelial cell's basolateral membrane. Likewise, *Demling and teammates* also localized RAGE at the human lung AT1 cell basolateral membrane. Thereby, RAGE prevalence in the normal lungs is majorly within the AT1 cells' basolateral membrane, now a consensual viewpoint. Apart from the AT1 cells, RAGE expression has been demonstrated in the lung endothelium, bronchial, and vascular smooth muscle, alveolar macrophages, leiomyocytes, and on the visceral pleural surface in bovine tissues. Multiple subsequent attempts demonstrated synergy with plentiful RAGE expression in the endothelial cells exhibiting vascular origin [1, 6 - 12].

## Receptor for Advanced Glycation End Products in Cardiovascular and Diabetic Complication(s)

Ruma Rani<sup>1,†</sup>, Parth Malik<sup>2,3,†</sup> and Tapan Kumar Mukherjee<sup>4,\*</sup>

<sup>1</sup> ICAR-National Research Centre on Equines, Hisar-125001, Haryana, India

<sup>2</sup> School of Chemical Sciences, Central University of Gujarat, Gandhinagar, Gujarat-382030, India

<sup>3</sup> Swarnim Startup & Innovation University, Bhoyan-Rathod, Gandhinagar-Gujarat, India

<sup>4</sup> Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India

**Abstract:** The Receptor for Advanced Glycation End Products (RAGE) has emerged as a pivotal player in the pathogenesis of cardiovascular and diabetic complications. An in-depth exploration of RAGE involvement in the disease processes, elucidating the molecular mechanisms, signaling pathways, and the associated pathological outcomes, is discussed. In diabetes, chronic hyperglycemia leads to the formation and accumulation of advanced glycation end products (AGEs), which activate RAGE and subsequently initiate a cascade of pro-inflammatory and pro-oxidative events. These processes contribute to the development and progression of diabetic vascular complications, including atherosclerosis, neuropathy, nephropathy, and retinopathy. In the cardiovascular system, RAGE activation promotes vascular inflammation, endothelial dysfunction, and vascular smooth muscle cell proliferation, all of which are critical in the pathogenesis of atherosclerosis and cardiovascular diseases. Furthermore, RAGE-mediated oxidative stress and inflammation have been implicated in the progression of heart failure and post-ischemic injury. Targeting RAGE signaling thereby emerges as a promising therapeutic approach to mitigate the detrimental effects of chronic hyperglycemia and vascular inflammation in diabetic and cardiovascular diseases. A comprehensive understanding of the multifaceted RAGE functions in cardiovascular complications such as atherosclerosis, peripheral arterial disease, atrial fibrillation, thrombotic disorder, myocardial infarction, vascular calcification, and the role of RAGE in diabetes-associated cardiac fibrosis, is discussed with a focus on therapeutic significance.

\* **Corresponding author Tapan Kumar Mukherjee:** Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India; E-mail: tapan400@gmail.com

† These authors contributed equally to this work.

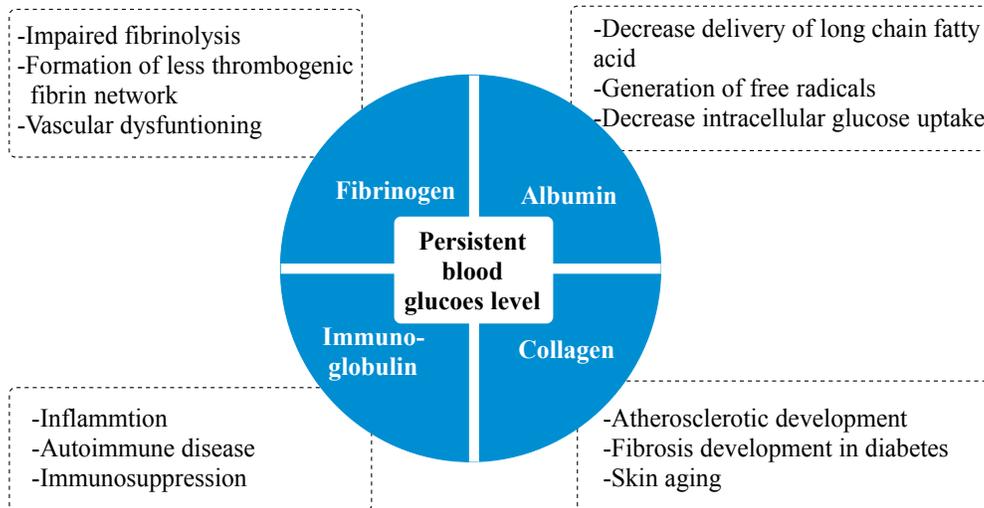
**Keywords:** Atherosclerosis, Atrial Fibrillation, Diabetic Nephropathy, Diabetic Retinopathy, Diabetic Neuropathy, Myocardial Infarction, Peripheral Arterial Disease, Receptor for Advanced Glycation End Products (RAGE), Vascular Calcification.

## INTRODUCTION

In type-1 and 2 diabetes (T1D, T2D), cardiovascular disease (CVD) squarely remains a leading cause of morbidity and mortality [1 - 4]. The detrimental impacts of consistently high plasma glucose on various organs vary based on the kind of cells and tissues involved. Vascular endothelial cells (ECs), for example, display high quantities of glucose transporter 1 (GLUT 1), making them more susceptible to the damaging effects of hyperglycemia due to the inability to restrict intracellular glucose concentrations. The increased glucose levels in the circulation, skin, and other tissues cause glycation, a non-enzymatic process, resulting in plasma proteins and glucose covalent adducts formation. Many diabetic complications are primarily caused by protein glycation [5]. Some structural and functional proteins, including collagen and those from plasma, may become glycated due to persistently high glucose extents [6]. The alteration of drug binding in plasma, platelet activation and the generation of oxygen free radicals, impaired fibrinolysis, and immune system functioning are the prominent harmful effects emanating from non-enzymatic modification of plasma proteins, such as albumin, fibrinogen, and globulins (Fig. 1) [5 - 7]. Conversely, structural collagen impairment modifies osteoblast differentiation, which results in skeletal fragility and bone remodeling [8, 9]. Increased extracellular matrix (ECM) formation and polyol pathway activation are the traits of diabetic phenotype that are acquired by renal mesangial cells over-expressing GLUT 1 [3]. The death rate for people with diabetes and myocardial infarction (MI) or stroke is almost twice as high, resulting in a projected 12-year reduction in life expectancy [10]. Important gaps in the treatment arsenal for diabetes and cardiovascular disease (CVD) remain, despite efforts to control blood pressure, cholesterol, and lifestyle factors. These hurdles highlight an urgent need for disease-modifying treatments and feasible cautions, *vis-à-vis* life threats.

One of the major problems of diabetes is accumulated glycation products [11, 12]. It has been discovered that the levels of intra- and extracellular AGEs in clinical and experimental models of diabetes are higher than in young, healthy controls [13, 14]. These correlative data infer a likely role of glycation in the pathophysiology of diabetes in disease advancement. All major biomolecules are affected by glycation; damage levels are predicted as 0.1% of basic phospholipids, 1 in 107 nucleotides on DNA, and 0.1-1% for lysine and arginine residues on proteins [15]. The extent of damage is likely to have detrimental effects. For

example, the production and build-up of protein AGEs can lead to metabolic malfunction. With the progressive glycation of arginine and lysine residues, charge neutralization can alter the protein structure and the consequent functional integrity [16]. In contrast to the non-glycated protein, glycated collagen is stiff and nonelastic [17, 18].



**Fig. (1).** Long-term diabetes with persistently high blood sugar causes structural and functional alterations in several bodily proteins, such as albumin, globulins, fibrinogen, and collagens. Glycation of these proteins is linked to the induction of harmful effects in the body.

The shift in charge distribution may also aggravate protein aggregation, such as lens crystalline-mediated cataract development in elderly with diabetes and other conditions [19, 20]. The function of a protein may also be affected by conformational changes, glycation of amino acid residues at substrate binding sites, and allosteric regulation of enzymes. For example, it has been demonstrated that glutamate dehydrogenase isolated from bovine liver exhibits decreased activity on methyl glyoxal-induced glycation of lys 126 and arg 463, affecting the enzyme's substrate binding capacity besides its allosteric activator (adenosine diphosphate, ADP), respectively [21].

Cell-ECM interactions are also impacted by the glycation of extracellular matrix (ECM) proteins. For example, EC detachment caused by methylglyoxal (MGO) reaction with arginine residues on the RGD and GFOGER motifs in the collagen integrin binding sites, interfered with cell-ECM interactions [7]. The formation of lipid glycation adducts, which increase membrane fluidity [22], may also have an impact on membrane interactions [23]. Glycation can occur in lipids with a free  $-NH_2$  group, like phosphatidylethanolamine, but not in those not having a free

## CHAPTER 9

## Receptor for Advanced Glycation End Products in Various Types of Cancers

Parth Malik<sup>1,2,†</sup>, Ruma Rani<sup>3,†</sup> and Tapan Kumar Mukherjee<sup>4,\*</sup>

<sup>1</sup> School of Chemical Sciences, Central University of Gujarat, Gandhinagar, Gujarat-382030, India

<sup>2</sup> Swarnim Startup & Innovation University, Bhoyan-Rathod, Gandhinagar-Gujarat, India

<sup>3</sup> ICAR-National Research Centre on Equines, Hisar-125001, Haryana, India

<sup>4</sup> Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India

**Abstract:** The receptor for advanced glycation end products (RAGE) was first isolated and characterized in the bovine lungs. Mammalian lungs express a relatively higher level of RAGE than other organs of the mammalian body. Physiologically, RAGE guards from lung cancer development owing to which, a diminished RAGE expression is implicated in the lung cancer complication. Opposed to this, a high-level RAGE expression is associated with the development of various cancers including breast, ovary, prostate, pancreatic, colon and colorectal, hepatocellular, melanoma, and neuronal. Interactions of RAGE and its multiple ligands, namely advanced glycation end products (AGE), high mobility group box protein 1 (HMGB1), S100/calgranulin, Mac 1, amyloid beta (A $\beta$ ) peptide, and others are involved in the complications of cancers. Besides their interactions with RAGE, RAGE ligands also independently aggravate the cancer-promoting actions. In cancer cells, the cellular events affected by RAGE include proliferation, survival, angiogenesis, autophagy, invasion, and metastasis. RAGE-ligands interaction aggravates inflammation and oxidative stress, leading to the propagation of various diseases including cancers.

**Keywords:** Apoptosis, Autophagy, Angiogenesis, Cancer, Invasion, Metastasis, Proliferation, RAGE, Survival.

### INTRODUCTION

In 1992, *Anna Marie Schmidt* and *associates* isolated, purified, and biochemically characterized the receptor for advanced glycation end products (RAGE) from the bovine pulmonary tissues [1]. Following this discovery, multiple studies including

\* Corresponding author Tapan Kumar Mukherjee: Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India; E-mail: tapan400@gmail.com

† These authors contributed equally to this work.

those of *Brett and colleagues*, analyzed the RAGE expression in embryonic and adult bovine, rat, and human tissues of various organs. While all major organs of the human body express RAGE, its maximum expression is noticed in the lungs. The study by *Brett and teammates* demonstrated that the bovine tissue's pulmonary vasculature, particularly endothelium and smooth muscle cells (SMCs) express RAGE. This study also detected RAGE expression in cardiomyocytes and mononuclear cells, including monocyte-derived macrophages. Considerable RAGE expression was also scrutinized in neonatal rat cardiomyocytes, neural tissues, and rat PC12 pheochromocytes [2]. The RT-PCR analysis of human cDNA by *Schlueter C and associates* revealed that alternative mRNA splicing is linked to tissue-specific RAGE distribution [3]. Many versions of RAGE mRNA are produced by alternative splicing, one of which is RAGE variant 1 (RAGEv1), which yields the majority of RAGE soluble form (known as sRAGE in the blood) and can bind a variety of RAGE ligands. Consequently, sRAGE functions as a decoy receptor, attenuating RAGE-driven cell signaling in inflammation and possibly resulting in carcinogenesis [4].

RAGE was not only detected for the first time in lung tissues [1] but its highest-level expression was also observed in the lung tissues [2]. Several investigations conducted after *Schmidt and colleagues* work, described the tissue and cell-specific expression of RAGE in the lungs. Although the initial research conducted by *Katsuoka and colleagues* located RAGE in lung epithelial type II cells [5], studies by *Demling, Shirasawa, and Fehrenbach* research groups demonstrated the exclusive RAGE expression in AT-I epithelial cells [6 - 8]. Significantly, neither AT-II epithelial nor capillary endothelial cells showed signs of RAGE expression in the investigations. Using quantitative immunoelectron microscopy, *Fehrenbach and colleagues* [7] for the first time, showed RAGE localization on the basal face of AT-I cell plasma membrane in rat and human lungs. Henceforth, other researchers also reported the RAGE expression in the basolateral membrane of AT-I epithelial cells [6, 8]. It is now widely accepted that the basolateral membrane of lung AT-1 cells exhibits the highest RAGE expression.

Structurally, RAGE is regarded as a cell surface immunoglobulin class of molecule [9] interacting with multiple ligands and is therefore characterized as a multi-ligand receptor. Further investigation herein, demonstrated a significant homology between the human RAGE sequence and the cell surface immunoglobulin class of molecules, including the cytoplasmic domain of B lymphocyte antigen (CD20), cell surface glycoprotein (MUC18, also known as CD146), and neural cell adhesion molecule (NCAM, also known as CD56). RAGE is therefore regarded as a molecule belonging to the cell surface immunoglobulin class [9]. Many physiological and pathological processes are ascribed to the interactions between RAGE and ligand(s). Full-length human

RAGE cDNA-transfected human HEK-293 cells were used by *Demling and colleagues* to examine the physiological role of RAGE in pulmonary tissues. Analysis revealed the transfected cell adhesion and dissemination in the kidney epithelial HEK-293 cell line are controlled by RAGE [8]. Almost 95% of pulmonary epithelial cells are characterized as AT1 type [10]. Studying the RAGE expression in rat lungs, *Lizotte and colleagues* observed progressive fetal growth with enhanced RAGE expression, wherein lung-RAGE expression was inhibited by hyperoxia. Monitoring the stimulation of AT-I epithelial cell adhesion and spreading (for pulmonary homeostasis) [8, 11], the investigators concluded that RAGE played a significant role in pulmonary homeostasis [11].

High-level RAGE expression is implicated in the pathogenesis of manifold pulmonary [12 - 14] and non-pulmonary diseases including various cancers. Altered RAGE expression is implicated in the complication of non-small cell cancers (NSCLCs) [15 - 19]. NSCLCs are considered the major type of lung cancer as almost 85% of lung cancers are characterized as NSCLCs. However, the role of RAGE in less common (~15%), small cell lung cancer (SCLC) complications, is not known. Several studies correlated a suppressed RAGE expression in the pulmonary tissues to aggravated NSCLC conditions. These findings concurred with the hypothesis that RAGE protects lung tissues from tumour susceptibility, strengthening the feasibility that the suppression of RAGE expression encouraged NSCLC development [20, 21]. However, erstwhile reports illustrate the RAGE contribution to pathophysiological events leading to lung cancer complications [22]. Additional investigation is required to delineate the specific role of RAGE in lung cancer development. However, the results of separate, independent investigations ascertained RAGE involvement in the complication of various cancers including those of breast, prostate, melanoma, and pancreatic. These studies examined the role of RAGE in the proliferation, survival, angiogenesis, autophagy, invasion, and metastasis of various cancer cells [23]. Interaction of RAGE with its manifold ligands aggravates inflammation and oxidative stress, resulting in various diseased conditions including cancers [24]. The dual action-mechanism of RAGE (growth-suppressive in the lung to growth-promoting in the breast, prostate, colon, *etc.*) appears to result from variations in the genetic regulation controlling: (a) location-dependent function; (b) spliced variant functional diversity; and (c) tissue-specific abundance of specific ligands.

The dynamic results of ligand-specific RAGE interactions remain a concern for researchers, even though the role of these interactions has been well studied in the control of homeostasis, inflammatory responses, angiogenesis, and carcinogenesis (in various malignancies) [25 - 28]. Augmenting the complexity, recent studies illustrate the diverse functional responses *vis-à-vis* varied ligand extents [29, 30]. The distinct outcomes attributed to genetic polymorphisms have also been

## Receptor for Advanced Glycation End Products in Neuronal Pathophysiology

Parth Malik<sup>1,2,†</sup>, Ruma Rani<sup>3,†</sup> and Tapan Kumar Mukherjee<sup>4,\*</sup>

<sup>1</sup> School of Chemical Sciences, Central University of Gujarat, Gandhinagar, Gujarat-382030, India

<sup>2</sup> Swarnim Startup & Innovation University, Bhoyan-Rathod, Gandhinagar-Gujarat, India

<sup>3</sup> ICAR-National Research Centre on Equines, Hisar-125001, Haryana, India

<sup>4</sup> Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India

**Abstract:** The receptor for advanced glycation end products (RAGE) is a multi-ligand receptor molecule expressed in the cells of the nervous system (neurons and glial cells). Compared to embryonic cells, RAGE expression is significantly decreased within the adult tissues, including the nervous system. Various RAGE ligands such as amyloid-beta peptide (A $\beta$ -peptide), high mobility group box protein 1 (HMGB1), S100/calgranulin, and advanced glycation end products (AGEs) are expressed by the cells of the nervous system. Several studies have predicted the role of RAGE in neurogenesis. Interaction of RAGE with its various ligands has been demonstrated as the responsible factor for complicating multiple diseased conditions such as Neuronal Differentiation and Outgrowth, Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD), Amyotrophic Lateral Sclerosis (ALS), Creutzfeldt-Jakob's Disease (CJD), Peripheral Neuropathies, Familial Amyloid Polyneuropathy (FAP), Spinal Cord Injury (SCI), and epilepsy. The interactions of RAGE with its ligands are critically dependent on the relative extents of inflammation and oxidative stress, controlling the various neurological disease manifestations. Redox sensitivity of such interactions is inferred by their treatment using targeted and sustainable antioxidant delivery at the affected regions. Besides targeting RAGE-ligand interactions *via* blocking RAGE expression may be useful against various neurological diseases.

**Keywords:** AGEs, A $\beta$ -peptide, HMGB1, Inflammatory and Oxidative stress, Multi-ligand receptor molecule, Neurogenesis, RAGE-ligand interactions.

\* Corresponding author Tapan Kumar Mukherjee: Amity Institute of Biotechnology, Amity University, New Town, Kolkata, West Bengal 700156, India; E-mail: tapan400@gmail.com

† These authors contributed equally to this work.

Tapan Kumar Mukherjee, Parth Malik & Ruma Rani (Eds.)  
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## INTRODUCTION

The nervous system is the network of nerve cells (neurons) and fibers that transmit nerve impulses between various parts of the body surrounded by many glial cells (the supporting cells of neurons). While neurons or nerve cells with their fibers are associated with the transmission of nerve signals, glial cells are implicated in supporting and nourishing neuronal cells. The receptor for advanced glycation end products (RAGE) is expressed in neuronal and glial cells both in the embryonic and adult stages, albeit to a lower extent in the latter. The multi-ligand receptor molecule RAGE binds with several ligands in neuronal cells such as amyloid-beta ( $A\beta$ )-peptide, high mobility group box protein 1 (HMGB1), S100/calgranulin, and advanced glycation end products (AGEs). The prevalence of RAGE and its ligands in the cells of the nervous system has been studied quite keenly from physiological and pathophysiological considerations. Several studies have predicted the involvement of RAGE in neurogenesis. However, a high-level expression of RAGE or its various ligands and subsequent enhanced extent of RAGE-ligand interactions, have been screened as the causative factors of various neurological disorders (NDs). For instance, accumulation and aggregation of  $A\beta$  peptide, one of the major RAGE ligands in the neuronal tissues induces the hyperphosphorylation of tau ( $\tau$ ) proteins, promoting the pro-inflammatory activation of microglia and supplementary neurological cells leading to synaptic loss and the consequent manifestation of Alzheimer's disease (AD). Similarly, investigations at multiple platforms have demonstrated aggravated AGE and RAGE extents in the frontal cortex and other brain regions, exhibiting enhanced vulnerability in the sufferers of Parkinson's disease (PD). The RAGE-ligand interactions are predicted to complicate PD. In Huntington's disease (HD), RAGE is upregulated in many affected brain regions, confining with the mutant Huntingtin (Htt), a prominent protein involved in HD pathogenesis. The other major neurological disorders (NDs) where RAGE and its various ligands are claimed to be involved in the propagation and complication, are Amyotrophic Lateral Sclerosis (ALS), Creutzfeldt-Jakob's Disease (CJD), Peripheral Neuropathies, Familial Amyloid polyneuropathy (FAP), Spinal Cord Injury (SCI), and epilepsy. High-level inflammation and oxidative stress generated by RAGE-ligand interactions are claimed as one of the major reasons for the enhanced severity of various NDs. Thus, several studies examined the efficacy of anti-RAGE molecules, including inhibitors against various RAGE ligands, besides suppressing the RAGE-ligand interactions as the treatment strategies for various NDs. This chapter discusses RAGE expression in neuronal cells, various RAGE ligands active in the neurological cells, and the NDs complicated by RAGE-ligand interactions. The experimental observations probing the efficacy of anti-RAGE/anti-RAGE ligand molecules affecting the RAGE-ligand interactions as

neuronal disease treatment are also recalled. However, these results are not conclusive since no clinical trials have been conducted based on them.

### **RAGE EXPRESSION IN NEURONAL AND SUPPORTING CELLS**

The mammalian nervous system consists of the brain, spinal cord, a complex network of cells, and associated fibers (dendrites, dendrons, axons, *etc.*). Neurons (also called nerve cells) and glial cells (providing physical and chemical support to neurons) constitute the nervous system. Neurons are associated with the transmission of nerve signals, through which these cells command a mammalian body, wherein abundant glial cells support and protect neuronal cells. In estimation, the human nervous system consists of nearly 360 billion non-neural glial cells and 90 billion nerve cells. There is a substantial level of interaction between neurons and glial cells, maintaining all biological functions of the nervous system [1 - 3].

RAGE expression varies with the specified cell nature and the corresponding embryogenic-developmental stage. In convention, RAGE is abundantly expressed in the developing embryo, where it serves as a receptor for amphoterin. The RAGE expression is downregulated in adult life. In a typical adult, while lungs and skin are the major locations of RAGE expression, a low-level RAGE expression is also detected in the brain [4, 5]. Several other studies subsequently confirmed a low-level RAGE expression in the neuronal tissues, particularly in those associated with various adult neuronal tissues. Certainly, excluding the skin and lungs where RAGE is exceedingly expressed throughout life, in the physiological environment, RAGE is expressed at meager extents in the adult central nervous system (CNS), glia, and neurons [6 - 9]. Based on the results of several investigations, it can now be confirmed that certain regions of CNS and PNS express RAGE. In the CNS, RAGE prevalence has been demonstrated in neurons, microglia, astrocytes, and pyramidal cells, with numerous studies establishing a decisive role of RAGE across the CNS [10, 11]. In peripheral nerves, RAGE is present in nerve bundles associated with blood vessels [12] and in axons [13]. In a notable effort, *Qin and colleagues* detected RAGE expression in the oligodendrocytes in response to oxidative stress. In this study, the investigators used primers and antibodies specific for rat RAGE, detected mRNA, and a 55-kDa RAGE protein using PCR and Western blotting respectively. The analysis further revealed stronger staining for membrane-localized RAGE oligodendrocytes in neonatal rats wherein 100  $\mu$ M hydrogen peroxide ( $H_2O_2$ ) treatment caused 55-kDa RAGE loss from the cell membrane, with the appearance of "soluble" 45-kDa RAGE in the culture medium, followed by restoration of RAGE expression to normal extents [9].

## SUBJECT INDEX

### A

- Acids 49, 106, 170, 296, 310, 311, 313, 441  
 glycyrrhetic 441  
 hyaluronic 49, 106
- Actions 270, 369, 393, 396  
 cancer-promoting 369  
 ligand-diversified tumorigenic 396  
 maleylacetoacetate isomerize 270  
 metastatic 393  
 proteolytic 393
- Activating 211, 343  
 immune cells 211  
 signaling pathways 343
- Activation, pro-inflammatory 409
- Activator protein 160
- Activities 97, 161, 201, 214, 215, 220, 222,  
 258, 264, 268, 270, 277, 329, 382, 388,  
 422, 424, 442  
 anti-inflammatory 442  
 citrate synthase 258  
 cytokine 201  
 enzymatic 97, 161, 220, 264, 329, 422  
 enzyme cofactor 382  
 glutathione reductase 268  
 growth factor 277  
 inflammatory 424  
 mediated cell-signaling 388  
 monomethyl arsenate reductase 270  
 neuronal 222  
 pro-inflammatory 215  
 telomerase 214  
 transcriptional 214
- Acute 192, 229, 241, 244, 245, 286, 287, 294,  
 295, 297, 300, 310, 313, 315, 317, 341,  
 375  
 coronary syndrome (ACS) 341  
 inflammation 244, 300  
 lung injury 192, 229, 241, 245, 286, 287,  
 294, 295, 375  
 respiratory distress syndrome (ARDS) 192,  
 229, 241, 245, 286, 294, 295, 297, 310,  
 313, 315, 317, 375
- AD-associated neuropathology 168
- Adeno-associated virus (AAV) 315
- Adhesion 42, 48, 67, 154, 230, 248, 273, 317  
 microbial 67  
 monocyte 273  
 pathogenic microbial 42
- Advanced 57, 275, 276, 277, 287, 428  
 oxidation protein products (AOPPs) 275,  
 276, 277, 287, 428  
 therapeutic medicinal products (ATMPs)  
 57
- Age 131, 150, 153, 154, 155, 156, 158, 163,  
 164, 168, 169  
 -altered protein damage 155  
 -altered proteins 150, 154, 168  
 -based chronic complications 164  
 -binding protein 153  
 -induced damage 168  
 -lipoprotein 131  
 -mediated autophagy 158  
 -mediated disorders 169  
 -modulated proteins 156, 163  
 proteins 169
- Aggressive frictional forces 277
- Aging-mediated complications 302
- Airway inflammation 230, 292, 293, 304  
 neutrophilic 230  
 smoke-induced 293
- Airway neutrophilia 294
- Albumin, serum protein 290
- Alzheimer's disease 164, 168, 174, 192, 198,  
 245, 254, 408, 409, 413, 429
- Amino acid 4, 121  
 nucleophilic 121  
 tryptophan 4
- Amyloid 198, 222, 223, 414, 432, 436, 444  
 fibril gatherings 436  
 precursor protein (APP) 198, 222, 223,  
 414, 432, 444

## Subject Index

Amyloidosis biology 437  
Amyotrophic lateral sclerosis 408, 409, 434  
Angiotensin-converting enzyme 57, 315  
Anti-diabetic agents 299  
Anti-phospholipid syndrome (APS) 338, 339  
Antigen-presenting cells (APCs) 35, 53, 69  
Antioxidant(s) 176, 242, 260, 261, 262, 263, 264, 268, 270, 271, 272, 274, 317, 330, 426, 431, 441, 442, 443  
agents 176  
catalysed reactions 263, 264  
food-derived 242, 261  
homeostasis 260  
natural 271, 317  
Aortas, thoracic 156  
Apoptosis 214, 215, 259, 260, 261, 270, 316, 317, 342, 382, 384, 385, 386, 387, 389, 390  
cardiomyocyte 342  
inhibiting 386  
Arthritis, rheumatoid 35, 215, 225, 228, 241, 254, 275  
Asthmatic airway inflammation (AAI) 291  
Atherosclerosis 155, 156, 158, 166, 169, 170, 277, 326, 327, 331, 332, 333, 334, 335, 336, 337  
accelerated 331, 334  
diabetes-aggravated 277  
risk in communities (ARIC) 337  
Atherosclerotic lesions 155, 276, 332, 337  
diabetic 332  
Atomic force microscopy (AFM) 414  
Autofluorescence spectroscopy 142  
Autophagy 214, 391  
cancer cell 391  
oxidative stress-mediated 214

## B

Biochemical analysis tools 41  
Bladder carcinomas 392, 393  
BMC-induced 299, 300  
lung fibrosis 300  
pulmonary fibrosis 299  
Bone 226, 227, 230, 343  
morphogenesis 226, 227, 230  
morphogenetic protein 343  
Bone marrow 227, 332  
-derived macrophages (BMDMs) 332  
macrophages (BMMs) 227

## Glycosylation and Glycation in Health and Diseases 461

transplantation 332  
Brain 109, 111, 162, 166, 168, 218, 223, 410, 413, 425, 432, 433, 434, 438  
inflammation 438  
trauma 218  
Breast 259, 389, 390, 391, 393, 394  
adenocarcinoma 389, 391, 393  
cancer cells 259, 391  
cancer proliferation 259  
metastatic 390  
tumorigenesis 394

## C

Cancer(s) 208, 381, 389, 390, 391, 392  
cells, thyroid 391  
colorectal 208, 381, 389, 390, 392  
gastric 381  
Carbohydrate response element binding protein (ChREBP) 388, 389  
Carcinoma 381, 388, 389, 391, 392, 393, 394, 395  
hepatocellular 381, 388, 389, 391, 392, 393  
oral squamous cell 381  
pancreatic 394  
Cardiac 344, 345  
dysfunction 345  
fibrosis 344, 345  
Cardiogenic shock 341, 342  
Cardiomyopathies, diabetic 161, 344  
Ceramide glucosyltransferase 109  
Chemotherapeutic drugs 208  
Cholesteatoma pathogenesis 276  
Chromatographic assays 145  
Chromatography, gel filtration 29  
Chronic 108, 135, 152, 192, 215, 229, 230, 241, 245, 286, 287, 290, 292, 293, 294, 303, 312, 313, 314, 317, 318, 344, 353, 375, 411, 414  
bronchitis (CB) 192, 229, 241, 245, 287, 290, 317, 375, 411  
inflammation, sustaining 414  
inflammatory processes 303  
intravascular hemolysis 108  
kidney disease (CKD) 135, 152, 215, 344  
obstructive pulmonary disease (COPD) 192, 229, 230, 241, 245, 286, 287, 292, 293, 294, 312, 313, 314, 317, 318  
obtrusive lung disease 312  
renal dialysis 353

- Cigarette smoke (CS) 129, 131, 132, 258, 311, 314, 379
- Concomitant 52, 306, 395
- effects 395
  - fibrinolytic performance 52
  - inflammation 306
- Conditions, heart arrhythmia 337
- Congenital muscular dystrophies (CMDs) 102, 103
- Conjugated carbohydrates 1
- Connective tissue growth factor (CTGF) 171, 298, 345
- Coronary artery 152, 335, 340, 343
- bypass grafting (CABG) 343
  - disease (CAD) 152, 335, 340
- CVD disorders 340
- Cytokines 273, 350, 354, 388, 439, 443, 444
- immunosuppressive 388
  - inflammatory 273, 350, 354, 439, 443, 444
- D**
- Damage 168, 170, 343, 348, 352
- diabetes-associated vascular permeability 352
  - inflammatory 352
  - myocardial 343
  - neuronal 348
  - stress-induced 170
  - stroke-mediated neurological 168
- Death-associated protein kinases (DAPK) 214
- Degradation, proteolytic 4, 33
- Diabetes mellitus (DM) 128, 132, 134, 225, 260, 315, 329, 330, 354, 425
- Diabetic atherosclerosis 332, 334
- signaling-mediated 334
- Diabetic 162, 169, 327, 347, 348, 349, 350, 351, 352, 353, 354, 355, 436, 439
- kidney disease 351
  - nephropathy 327, 349, 353, 354, 355
  - neuropathy (DN) 327, 347, 348, 351, 354, 436, 439
  - polyneuropathy 350
  - retinopathy (DR) 162, 169, 327, 350, 352
  - sensorimotor neuropathy 436
- Diseases 123, 168, 215, 218, 220, 224, 260, 278, 338, 408, 438, 439
- aging-related 168
  - autoimmune 215
  - inflammatory 220, 438
  - metabolic 224
  - neurological 408, 439
  - non-communicable 260, 278
  - psychiatric 218
  - respiratory 123
  - thrombotic 338
- Disorders 58, 135, 137, 156, 158, 197, 198, 212, 240, 260, 265, 303, 326, 331, 338, 339, 346, 419, 433
- autosomal recessive 303
  - cardiovascular 135, 156, 197, 198, 240, 260, 265, 419
  - chronic autoimmune 212
  - inflammatory brain 137
  - life-threatening autoimmune 58
  - metabolic 346
  - neurodegenerative 158, 433
  - neuropsychiatric 137
  - thrombotic 326, 331, 338, 339
- DNA 161, 162, 167, 329
- injuring protein 161
  - methylation 161, 162
  - mutations 167
  - polymerase 167, 329
- Dysfunction 93, 98, 249, 307, 309, 310, 333, 334, 434
- chronic lung allograft 310
  - metabolic 333, 334
  - mitochondrial 434
  - neurological 93
  - pulmonary 309, 310
- E**
- Electrophoresis 29, 149
- Electropositive topography 241
- Electrospray technique 28
- Enzyme(s) 41, 108, 143, 146, 147, 148, 210, 266, 301, 312, 313, 316
- dysfunctional 108
  - erythrocytic 266
  - glycosylation-related 41
  - linked immunosorbent assay (ELISA) 143, 146, 147, 148, 210, 301, 312, 313, 316
- Erythroleukemia 389
- F**
- Fabry disease 109, 110
- Fatty acids biosynthesis 258

## Subject Index

Fibrillar transthyretin binding 437  
Fibrinolysis 338  
Fibroblast growth factor (FGF) 59, 60, 300, 421, 422  
Fragment antigen binding (FAB) 35  
Fusion proteins 36  
glycosylated 36

**G**

Galactosyltransferases 106  
Gas chromatography 143, 148  
Gastric aspiration 295  
Gaucher disease 109, 110  
Genetic mutations 84, 85, 86, 87, 88, 89, 91, 92, 96, 97, 98, 101, 103, 104, 114  
Glucose 139, 327  
oxidation 139  
transporter 327  
Glutathione 126, 264, 268  
reductase 126, 268  
transferase 264  
Glycan-binding proteins (GBPs) 42, 66, 68  
Glycoamidase 30  
Growth 391, 413, 417, 426  
breast cancer 391  
cytoplasmic 417  
neuronal 413, 426  
Growth factors (GF) 5, 44, 56, 59, 62, 64, 220, 221, 300, 305, 352, 388, 428, 437  
fibroblast 59, 300  
glycosylated 44  
neurotrophin 437  
Gut microbiota 439, 443

## H

Heart disease 308, 331  
congenital 308  
Heart failure 135, 293, 341  
chronic 135, 341  
congestive 293  
Homeostasis, pulmonary 289, 371  
Horseradish peroxidase 26  
Human leukocyte antigen (HLA) 192  
Huntington's disease (HD) 198, 408, 409, 433, 434  
Hypertension, pulmonary 241, 245, 286, 308

## Glycosylation and Glycation in Health and Diseases 463

## I

Imbalances 91, 93, 103, 115, 260, 346  
metabolic 115  
Immune 47, 53, 54, 102, 105, 112, 202, 249, 387, 388, 417  
responses 47, 53, 54, 102, 105, 112, 202, 249, 387, 388, 417  
Immune system 35, 67, 94, 115, 170, 205, 327, 388  
dysfunction 115  
dysregulation 94  
humoral 35  
Immunolectron microscopy 210  
Immunofluorescence microscopy 210  
Induction 158, 160, 167, 208, 223, 254, 260, 273, 314, 317, 328, 342, 354, 379, 384, 423  
apoptotic 208, 260, 314, 423  
autophagic 384  
comprising apoptotic gene 223  
vascular disease 254  
Infarction 168, 170, 326, 327, 331, 339, 340  
myocardial 170, 326, 327, 331, 339, 340  
Infection damages 307  
Infections 67, 68, 94, 109, 266, 214, 271, 278, 307, 335, 354, 417  
bacterial 214, 307  
malarial 67  
microbial 307  
myocardial 266  
polymicrobial 307  
Inflammation 94, 129, 137, 274, 295, 346, 350, 434  
immune system-related 94  
mediated 434  
metabolic 346  
neutrophil-derived 295  
pulmonary 129  
renal 274  
retinal 350  
rheumatic 137  
Inflammatory 228, 241, 254, 436  
demyelinating polyneuropathy 436  
kidney disease 228, 241, 254  
Inflammatory bowel 228, 229, 241, 245, 254  
disease (IBD) 228, 229, 241, 245  
syndrome 254  
Inflammatory disorders 197, 198, 307, 315  
acute 307

- chronic 315
- Ischemia 309, 411
  - reperfusion injury (IRI) 309
  - transient brain 411
- K**
- Kidney 93, 110, 171
  - dysfunction 93, 110
  - transplantation 171
- L**
- Limb ischemia, non-diabetic hind 336
- Lipid 268, 423
  - homeostasis 423
  - hydroperoxides 268
- Liquid chromatography (LC) 8, 28, 29, 143, 145, 148
- LPS 68, 151, 203, 205, 206, 210, 273, 295, 310, 316, 317, 411
  - binding protein 210
  - induced autophagy 317
- Lung 226, 241, 245, 301, 302, 375
  - disorders 241, 245
  - fibroblasts 301
  - fibrosis 302
  - neoplasm 375
  - organogenesis 226
- Lung cancer 192, 289, 310, 315, 317, 369, 371, 376, 377, 378, 379, 381, 396
  - actions 396
  - authentic 377
  - complications 369, 371
- Lysosomal 101, 109, 111, 206
  - storage disorders (LSDs) 101, 109, 111
  - thiol reductase 206
- M**
- Macrophage inflammation 212
- MAPK 218, 219, 295, 339, 344, 378, 387, 389, 390, 414, 421, 432
  - activation 378, 387, 414, 432
  - pathways 218, 219, 339, 344, 389, 390, 421
  - signaling pathways 295
- Mass spectrometry (MS) 23, 25, 27, 28, 29, 57, 143, 145, 148, 419
- Matrix metallo proteinases (MMPs) 59, 341, 382, 390, 391, 393, 394, 395
- Melanoma, malignant 216
- Membrane 4, 17, 47, 210
  - glycoproteins 4, 47
  - proteins 17, 210
- Metabolic 134, 135, 158, 161, 162, 346
  - memory 161, 162
  - syndrome 134, 135, 158, 346
- Migration, neuronal 55, 91, 417
- Mitochondrial 171, 386
  - pathway 386
  - proteins 171
- Mitogen-activated protein kinase (MAPKs) 276, 315, 343, 351, 352, 382, 388, 389, 390, 391, 392, 394, 395, 441
- MS techniques 37
- Myelodysplastic syndromes 109
- Myeloid 170, 326, 327, 331, 333, 338, 339, 340, 341, 342, 388
  - derived suppressor cells (MDSCs) 388
  - infarction (MI) 170, 326, 327, 331, 333, 338, 339, 340, 341, 342
- N**
- Necrosis 212, 384
- Neoadjuvant chemoradiotherapy 208
- Neurodegenerative diseases 134, 225, 419, 432, 433, 445
- Neurological disorders (NDs) 85, 114, 123, 409, 421, 426, 429, 438, 439, 440, 445
- Neuronal dysfunctions 91, 436
- Next-generation sequencing technologies 86
- Non-small cell lung cancers (NSCLCs) 190, 192, 286, 287, 371, 372, 374, 376, 378, 380, 381, 392, 396
- Nuclear magnetic resonance (NMR) 440
- O**
- Oxidative damage, mitochondrial 206
- P**
- Parkinson's 137, 228, 408, 409, 421, 432, 440, 445
  - disease 137, 228, 408, 409, 421, 432, 440
  - disorders 445
- Pathways, inflammatory 412, 434
- Peptide 53, 64, 69, 126, 151, 171, 222, 223, 230, 369, 372, 409, 430

## **Subject Index**

antigenic 69  
cytosolic 64  
neurotoxic 223  
Peripheral arterial disease (PAD) 326, 327, 335, 336  
Platelet-derived growth factor (PDGF) 300, 383  
Populations, gut microbial 50  
Positron emission tomography (PET) 430  
Process, neurodegenerative 432, 434  
Prostaglandin isomerase 270  
Protein(s) 1, 19, 26, 32, 33, 37, 41, 53, 100, 172, 173, 274, 419, 432, 435  
  foreign 53  
  genes 419  
  glycosylation 1, 26, 32, 33, 37, 41, 100, 172, 173  
  immune 274  
  lysosomal 19  
  neurofilament 432, 435  
Protein glycation 124, 132, 139, 166, 327, 329  
  non-enzymatic 166  
Pulmonary 275, 298, 299, 300, 301, 308, 310, 311, 318  
  artery smooth muscle cell (PASMC) 308  
  disorders 310, 311, 318  
  fibrosis 275, 298, 299, 300, 301  
Pulmonary arterial 192, 308  
  hypertension (PAH) 192, 308  
  pressure (PAP) 308

**R**

Radiations 129, 131  
  ionizing 129, 131  
  non-ionizing 131  
Reaction 4, 37, 53, 69, 381  
  deglycosylation 37  
  immune 53, 69  
  immunological 4  
  ligase detection 381  
Reactive 121, 123, 129, 215, 240, 242, 244, 251, 252, 253, 254, 256, 259, 260, 262, 273, 314, 423  
  oxygen nitrile species (RONS) 314  
  oxygen species (ROS) 121, 123, 129, 215, 240, 242, 244, 251, 252, 253, 254, 256, 259, 260, 262, 273, 423  
Receptor tyrosine kinases (RTKs) 305  
Recombination-activating genes (RAG) 213

## **Glycosylation and Glycation in Health and Diseases 465**

Renal 354  
  failure 354  
  hemodynamics 354  
Respiratory syncytial virus (RSV) 306  
Retinopathy, diabetic 162, 169, 327, 350, 352  
Rheumatoid arthritis (RA) 35, 215, 225, 228, 241, 254, 275

## **S**

Screening 411  
  immunofluorescence 411  
  immunohistochemistry 411  
SDS-PAGE to screen for glycosylation 24  
Signal 11, 32, 215, 438  
  recognizing particles (SRPs) 11  
  transduction pathways 32, 215, 438  
Single nucleotide polymorphisms (SNPs) 194, 380  
Skin autofluorescence 121, 135, 144  
Spectrofluorimetric methods 148  
Sterol regulatory element-binding proteins (SREBPs) 214  
Stress-activated protein kinases (SAPk) 392

## **T**

Therapies, substrate reduction 101  
Thin layer chromatography (TLC) 27  
Thrombosis, cerebral venous 109  
Thrombotic diseases (TD) 338  
Thyroid carcinoma 392  
Tissue inhibitors of metalloproteinase (TIMPs) 341  
Transferrin isoelectric focusing (TIEF) 95  
Transforming growth factor (TGF) 59, 298  
Transverse aortic constriction (TAC) 345  
Tumor(s) 160, 206, 208, 211, 215, 216, 270, 375, 387, 432  
  cell migration 375  
  microenvironment 208, 387  
  necrosis factor (TNF) 160, 206, 211, 215, 270, 432  
  neurogenic 216

## **U**

Ultra-high-pressure liquid chromatography (UHPLC) 143, 148  
UV radiations 260

**V**

Vascular 5, 154, 158, 192, 218, 225, 317, 351,  
352, 382, 388, 390, 392, 393, 395  
complications, neurological 192  
endothelial growth factor (VEGF) 5, 158,  
351, 352, 382, 388, 390, 392, 393, 395  
osteogenesis 154  
smooth muscle cells (VSMCs) 154, 158,  
218, 225, 317

**W**

Western blot analysis 313  
Whole 96  
-exome sequencing (WES) 96  
-genome sequencing (WGS) 96



## **Tapan Kumar Mukherjee**

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Tapan Kumar Mukherjee did Ph.D. in physiology from Bose Institute, DST, Govt. of India. He completed post-doctoral training at CCMB, CSIR Govt. of India, and UCLA-USA. He has faculty experience at the University of Utah, Salt Lake City, USA, and MMU, Mullana, India. In the capacity of a visiting scientist, he has visited the University of Utah USA, KRIBB South Korea, and NUS Singapore. His primary research involves deciphering the role of cell-signaling molecules in cancer and cardiovascular diseases. He is working as a professor at Amity University-Kolkata, India.



## **Parth Malik**

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Parth Malik holds a B. Tech in biotechnology and M. Tech in nano science and technology with a broad specialization in nanobiotechnology. He completed M. Phil and Ph.D. from the Central University of Gujarat, with his research focus on "Sustainable fabrication of low energy emulsions for modulating the antioxidant efficacy of curcumin". He has been actively engaged in research and academics since 2018, teaching food chemistry, nanobiotechnology and completing a DST sponsored project on Desalination enabled KNO<sub>3</sub> recovery.



## **Ruma Rani**

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Ruma Rani did master's in medical biotechnology from Maharshi Dayanand University, Rohtak, India. She received a distinguished "INSPIRE" fellowship from DST, New Delhi, to complete her doctorate in biotechnology from GJUS&T, Hisar. She has completed CSIR-Postdoctoral Research Associateship and SERB-National Postdoctoral Fellow project at ICAR-NRCE, Hisar. Her research interests include nanoparticle synthesis and characterization, nanodrug delivery, pharmacological in vitro and in vivo evaluation, molecular diagnostics, and recombinant technology. She has published research papers in reputed international journals and attended many national and international conferences.