

Contents

Preface *xiii*

1	Diet-Based Microbiome Modulation: You are What You Eat	<i>1</i>
	<i>Jiashu Li, Zeyang Qu, Feng Liu, Hao Jing, Yu Pan, Siyu Guo, and Chun Loong Ho</i>	
1.1	Introduction	<i>1</i>
1.1.1	Microbiome Diversity in Human Body	<i>1</i>
1.1.1.1	Oral Microbiome	<i>2</i>
1.1.1.2	Gastrointestinal Microbiome	<i>3</i>
1.1.1.3	Skin Microbiome	<i>4</i>
1.1.1.4	Respiratory Microbiome	<i>5</i>
1.1.1.5	Urogenital Microbiome	<i>5</i>
1.1.2	Elements that Influence Microbiome Development	<i>5</i>
1.1.2.1	Prebiotics	<i>6</i>
1.1.2.2	Probiotics	<i>6</i>
1.1.2.3	Diet and Nutrition	<i>7</i>
1.1.3	Current Approaches Employed in Studying the Human Microbiome	<i>7</i>
1.2	Dietary Lifestyle Variation Affecting Host Microbiome	<i>8</i>
1.2.1	Dietary Role in Shaping the Microbiome	<i>8</i>
1.2.1.1	Protein and Polypeptides	<i>8</i>
1.2.1.2	Soluble Saccharides	<i>9</i>
1.2.1.3	Dietary Fibers	<i>9</i>
1.2.1.4	Lipids	<i>10</i>
1.2.2	The Socioeconomic Impact on Diet-Related Microbiome Changes	<i>11</i>
1.2.3	Age Groups and Dietary-Related Microbiome Changes	<i>13</i>
1.2.4	Continental Dietary Difference and Its Effect of the Local Microbiome	<i>15</i>
1.2.4.1	Asia	<i>15</i>
1.2.4.2	Europe	<i>15</i>
1.2.4.3	Australia	<i>16</i>
1.2.4.4	Africa	<i>16</i>

1.2.4.5	South America	16
1.2.4.6	North America	17
1.3	Dietary Modulation of Microbiome for Disease Treatment	17
1.3.1	Infection	17
1.3.1.1	Fecal Microbiota Transplantation (FMT)	17
1.3.1.2	Prebiotic-, Diet-, and Probiotic-Mediated Prevention of Pathogenic Infections	19
1.3.2	Inflammatory Disease	20
1.3.3	Cancer	21
1.3.4	Psychological Disease	22
1.3.4.1	Autism Spectrum Disorder	22
1.3.4.2	Neurodegenerative Diseases	23
1.3.5	Metabolic Disorder	23
1.3.5.1	Obesity	23
1.3.5.2	Diabetes	24
1.3.5.3	Non-alcoholic Fatty Liver Disease (NAFLD)	24
1.4	Challenges and Opportunities	25
1.4.1	Limitations in the Field	25
1.4.2	Current Microbiome Project Supporting Infrastructures	25
1.4.2.1	International and Local Initiatives	25
1.4.2.2	Global Foundations	27
1.5	Concluding Remarks	27
	Acknowledgments	28
	References	28
2	Microbiome Engineering for Metabolic Disorders	47
	<i>Nikhil Aggarwal, Elvin W. C. Koh, Santosh Kumar Srivastava, Brendan F. L. Sieow, and In Young Hwang</i>	
2.1	Introduction	47
2.2	Microbiome Engineering for Diabetes and Obesity	49
2.2.1	Microbiome Engineering for the Hypoglycemic Effect to Treat Diabetes and Obesity	50
2.2.2	Microbiome Engineering for Immune Modulation to Treat Diabetes	52
2.3	Microbiome Engineering to Modulate Gut–Liver Axis	54
2.3.1	Microbiome Engineering to Modulate Ammonia Metabolism	54
2.3.2	Microbiome Engineering to Modulate Phenylalanine Metabolism	55
2.3.3	Microbiome Engineering to Modulate Bile-Salt Metabolism	56
2.3.4	Microbiome Engineering to Modulate Fat Metabolism	57
2.4	Microbiome Engineering for Cardiovascular Diseases	58
2.4.1	Gut Microbiome Interventions for Cardiovascular Diseases	59

2.4.2	Role of Microbiome-Derived TMAO in Cardiovascular Diseases	60
2.5	Microbiome Engineering to Modulate Gut–Brain Axis	61
2.5.1	Exploratory Studies on the Development of Psychobiotics	64
2.6	Clinical Translation of Live Biotherapeutic Products	65
2.7	Conclusion and Future Directions	76
	References	76
3	Repurposing Microbes for Therapeutic Applications in Humans	93
	<i>Kangsan Kim, Donghui Choe, Minjeong Kang, Bong Hyun Sung, Haseong Kim, Seung-Goo Lee, Dae-Hee Lee, and Byung-Kwan Cho</i>	
3.1	Introduction	93
3.2	A Brief Overview of Microbiota and Human Health	94
3.2.1	Interactions Between Microbes and Their Compositions Affect the Host Metabolic Status	95
3.2.2	Host–Microbe Interactions Constitute an Essential Part of Host Metabolism	97
3.3	Systems Biology Approach to Analyze the Gut Microbiota Functions	98
3.3.1	Rational Design of Gut Microbiome Editing Strategies	98
3.3.2	High-Throughput Data-Driven Understanding of Gut Microbiota	100
3.4	Engineering Microbiome to Treat Diseases	102
3.4.1	Strain Selection for Microbiome Engineering	102
3.4.2	Engineering Microbes to Sense and Respond to Disease-Related Perturbations	103
3.4.3	Engineering Microbes to Express Therapeutic Proteins for Disease Treatment	109
3.5	Perspectives and Conclusion	111
	References	111
4	Modulating Residence Time and Biogeography of Engineered Probiotics	121
	<i>Rana Said, Zachary J. S. Mays, and Nikhil U. Nair</i>	
4.1	Introduction	121
4.2	Adhesion Mechanisms	122
4.3	Adhesion Modulation	125
4.4	Functional Encapsulations and Biofilms that Modify Gastrointestinal Dynamics of Probiotics	126
4.5	Metabolic Engineering to Modulate Gut Adaptation	128
4.6	Conclusions	129
	References	130

5	Microbiome Engineering for Next-Generation Precision Agriculture	<i>137</i>
	<i>Mohd Firdaus Abdul-Wahab, Shruti Pavagadhi, Hitesh Tikariha, and Sanjay Swarup</i>	
5.1	Background	137
5.2	Systems Approach to Microbiome Engineering	139
5.2.1	DBTL Framework for Microbiome Engineering	139
5.2.2	Computational Tools for Robust Microbiome Engineering	142
5.2.3	Genome-Scale Metabolic Modeling	143
5.3	Synthetic Biology for Genome and Genetic Engineering of Phytobiomes	144
5.4	Conclusion and Future Perspectives	146
	Acknowledgments	148
	References	148
6	Biological Sensors for Microbiome Diagnostics	<i>155</i>
	<i>Amy M. Ehrenworth Breedon, Kathryn R. Beabout, Heidi G. Coia, Christina M. Davis, Svetlana V. Harbaugh, Camilla A. Mauzy, M. Tyler Nelson, Roland J. Saldanha, Blake W. Stamps, and Michael S. Goodson</i>	
6.1	Introduction	155
6.1.1	The Malleable Microbiome	155
6.1.2	Engineered Probiotics	155
6.2	Diagnosing the Microbiome	156
6.2.1	Microbiome Analyses	156
6.2.1.1	Small Subunit rRNA Analysis	156
6.2.1.2	Metagenomics and Metatranscriptomics	157
6.2.1.3	Proteomics and Metabolomics	157
6.2.2	Considerations and Future of Microbiome Diagnosis	158
6.3	Types of Biosensors	159
6.3.1	Riboswitches	159
6.3.1.1	Riboswitches and Their Regulatory Mechanisms	160
6.3.1.2	Design and Selection of Synthetic Riboswitches	160
6.3.1.3	Riboswitches in Molecular Detection of Microbiome Metabolites	161
6.3.2	Transcription Factors	163
6.3.2.1	Transcription Factor Mining	163
6.3.2.2	Engineering Transcription Factors	164
6.3.2.3	Applications of Transcription Factors	165
6.3.3	Two-Component Systems	166
6.3.3.1	Introduction to Two-Component Systems	166
6.3.3.2	Expression of Natural TCS Systems for Gut Diagnostics	166

6.3.3.3	Engineering TCS-Based Sensors for the Microbiome	167
6.3.4	G Protein-Coupled Receptors	168
6.3.4.1	GPCRs and the Gut Microbiome	168
6.3.4.2	GPCRs Engineered Into Yeast	168
6.3.4.3	Recent Advances in Yeast GPCR-Based Sensors	170
6.4	Testing and Utilizing Engineered Biosensors	171
6.4.1	Cell-Free Protein Expression Systems (CFPS) for Biosensing	171
6.4.2	<i>In Vitro</i> Testing	173
6.4.2.1	<i>In Vitro</i> Models	174
6.4.2.2	Organ-on-a-Chip	174
6.4.2.3	<i>In Vitro</i> Host–Microbe Characterization	174
6.4.3	Examples of Engineered Microbes	176
6.4.3.1	Identifying Microbiome Changes <i>In Situ</i>	176
6.4.3.2	Engineered Microbes for Disease Diagnostics	176
6.4.3.3	Cancer	177
6.4.3.4	Inflammatory Bowel Disease	178
6.4.3.5	Infection	178
6.4.3.6	Future Translation	178
6.5	Conclusions/Summary	179
	Acknowledgments	180
	References	180

7	Principles, Tools, and Applications of Synthetic Consortia Toward Microbiome Engineering	195
	<i>Eliza Atkinson, Alice Boo, Huadong Peng, Guy-Bart Stan, and Rodrigo Ledesma-Amaro</i>	
7.1	Introduction	195
7.2	Advantages of Labor Division via Synthetic Microbial Consortia	197
7.2.1	Providing Optimal Conditions	198
7.2.2	Reducing the Metabolic Burden on the Host	198
7.2.3	Reducing Crosstalk and Competition Within Synthetic Pathways	199
7.3	Tools for Engineering Synthetic Consortia	200
7.3.1	Genetic Manipulation Tools	200
7.3.2	Cell-to-Cell Communication	200
7.3.3	External and Intercellular Signal Molecules for Regulating Gene Expression and Population Composition	201
7.3.4	Secretion and Exchange of Metabolites	201
7.3.5	Analysis Tools	202
7.3.6	Computational Models	202
7.3.6.1	Dynamic/Deterministic Models	202
7.3.6.2	Agent-Based Models	203

7.3.6.3	Stoichiometric and Genome-Scale Metabolic Models	203
7.4	Engineering Syntrophy	205
7.5	Engineering Population Control	206
7.6	Synthetic Microbial Consortia and the Human Microbiome	207
7.7	Conclusions and Future Perspectives	208
	References	209
8	Fecal Microbiota Transplantation for Microbiome Modulation: A Clinical View	<i>Peter C. Konturek, Thomas Hess, Walburga Dieterich, and Yurdagül Zopf</i>
8.1	Introduction	219
8.2	Fecal Microbiota Transplantation (FMT)	219
8.2.1	Recruitment of Potential Donors	220
8.2.2	Administration of FMT	220
8.2.3	Safety	220
8.3	Clinical Application of Fecal Microbiota Therapy	222
8.3.1	<i>C. difficile</i> Infection (CDI)	222
8.3.2	Inflammatory Bowel Disease	223
8.3.3	FMT as a Therapeutic Option to Eradicate Highly Drug-Resistant Enteric Bacteria Carriage	224
8.3.4	FMT and Irritable Bowel Syndrome	224
8.3.5	FMT and Slow-Transit Constipation	225
8.3.6	FMT and Liver Diseases	225
8.4	FMT – Novel Indications	226
8.4.1	Chemotherapy-Induced Diarrhea	226
8.4.2	Obesity and Metabolic Syndrome	227
8.4.3	Graft-versus-Host Disease (GvHD)	227
8.4.4	Autoimmune Diseases	227
8.4.5	Neuropsychiatric Disorders	228
8.5	Conclusion	228
	References	228
9	Maternal Microbiota as a Therapeutic Target	<i>Ferit Saracoglu</i>
9.1	Introduction	233
9.2	Human Maternal Microbiota	233
9.2.1	Oral Microbiota	233
9.2.2	Vaginal Microbiota	234
9.2.3	Endometrial Microbiome	234
9.2.4	Gut Microbiome	236
9.2.4.1	Maternal Gut Microbiome and Immune Functions	236

9.2.4.2	Gut and Brain Axis	238
9.2.4.3	Epigenetic Regulation of Gut Microbiota	238
9.2.5	Placental Microbiome and Meconium	239
9.3	Maternal Microbiota and Health	240
9.3.1	Developmental Origins of Adult-Onset Diseases: Barker Hypothesis	240
9.3.2	Maternal Microbiota and Obesity	240
9.3.2.1	Maternal Diet and Gut Microbiota	240
9.3.2.2	Body Mass Index, Insulin Resistance, and Obesity in Pregnancy	241
9.3.2.3	Childhood Obesity	241
9.3.3	Miscarriages and Microbiome	242
9.3.4	Postpartum Microbiome	242
9.3.4.1	Mode of Delivery	242
9.3.4.2	Vaginal Seeding	243
9.3.5	Maternal Microbiota and Gestational Age at Birth	243
9.3.6	Maternal Microbiota and Maternal Inflammation and Intrauterine Infections	244
9.4	Human Milk Microbiota and Infant Health	245
9.5	Drug Treatment, Unhealthy Conditions, and Microbiome	247
9.5.1	Perinatal Antibiotic Treatment	247
9.5.2	Smoking	249
9.5.3	Stress Under Pregnancy	249
9.5.4	Autism Spectrum Disorders	250
9.5.5	Critical Illness of Newborns	250
9.6	Probiotic and Prebiotic Therapies as Modulators of Microbiome	250
	References	252
10	Transcription Factor-Based Biosensors and Their Application in Microbiome Engineering	277
	<i>Seong Keun Kim, Seung Gyun Woo, Tae Hyun Kim, Seong Hyun Park, Jin Ju Lee, A Young Park, So Hyung Oh, Seong Kun Bak, Seung-Goo Lee, and Dae-Hee Lee</i>	
	Summary	277
10.1	Design: TF-Based Biosensors	278
10.1.1	Transcriptional Repressors	278
10.1.2	Transcriptional Activators	282
10.1.3	One-Component Regulatory System or Two-Component Regulatory System	283
10.1.4	Types of Output Modules	284
10.1.5	Layered Genetic Circuits	285
10.2	Build: TF-Based Biosensors	286
10.2.1	Construction of Genetic Circuits	286

10.2.1.1	Gene Synthesis	287
10.2.1.2	Restriction Enzyme–Based Cloning	287
10.2.1.3	Gibson Assembly	288
10.2.2	Chassis	288
10.3	Test: TF-Based Biosensors Application in Microbiome	289
10.3.1	Diagnostics	289
10.3.2	Therapeutics	291
10.3.3	Biocontainment	292
10.4	Learn: Strategies for TF-Based Biosensor Improvement	293
10.5	Conclusions	294
	List of Abbreviations	294
	Acknowledgments	295
	References	295
	Index	305