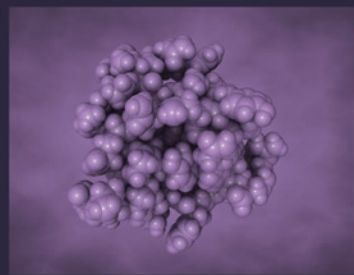


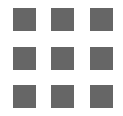
Unlocking Sirtuins

Cellular Biology to Translational Research



Edited by
Pranav Kumar Prabhakar
Sumel Ashique





Unlocking Sirtuins

This page intentionally left blank



Unlocking Sirtuins

Cellular Biology to Translational Research

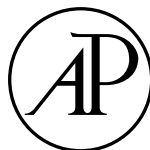
Edited by

Pranav Kumar Prabhakar

Department of Biotechnology, School of Engineering and Technology,
Nagaland University, Meriema, Kohima, Nagaland, India

Sumel Ashique

Department of Pharmaceutical Technology, Bharat Technology,
Uluberia, West Bengal, India



ACADEMIC PRESS

An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States

Copyright © 2026 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

For accessibility purposes, images in electronic versions of this book are accompanied by alt text descriptions provided by Elsevier. For more information, see <https://www.elsevier.com/about/accessibility>.

Books and Journals published by Elsevier comply with applicable product safety requirements. For any product safety concerns or queries, please contact our authorised representative, Elsevier B.V., at productsafety@elsevier.com.

Publisher's note: Elsevier takes a neutral position with respect to territorial disputes or jurisdictional claims in its published content, including in maps and institutional affiliations.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-443-45380-9

For Information on all Academic Press publications
visit our website at <https://www.elsevier.com/books-and-journals>

Publisher: Megan Ball
Acquisitions Editor: Michelle Fisher
Editorial Project Manager: Ashavari Bhattacharya
Production Project Manager: Sathyavani Deivasigamani
Cover Designer: Venkatraman Gopalakrishan

Typeset by MPS Limited, Chennai, India





Contents

List of contributors xv

Preface xix

Part 1 Introduction to sirtuins

1. Sirtuin proteins: structure, functions, and evolutionary insights	3
<i>Neetu Sachan, Prakhar Varshney, Phool Chandra and Pradeep Singh</i>	
1.1 Introduction	3
1.2 Historical perspective: from silent information regulator 2 to human sirtuins	4
1.3 Structural biology of sirtuins	6
1.4 Classification and subcellular localization	7
1.5 Tissue-specific sirtuin expression and function	9
1.6 Physiological functions	13
1.7 Sirtuins in health and disease	15
1.8 Sex and age-related differences in sirtuin function	17
1.9 Evolutionary insights	22
1.10 Biomarkers to track sirtuin-targeted therapy efficacy	23
1.11 Environmental and lifestyle influences on sirtuins	26
1.12 Translational applications	29
1.13 Future perspectives and challenges	30
1.14 Conclusion	31
References	33

2.	Nicotinamide adenine dinucleotide-dependent enzymatic mechanisms and nicotinamide adenine dinucleotide precursors (nicotinamide mononucleotide, nicotinamide riboside)	43
	<i>Zahid Ahmad Thoker, Lovleen Marwaha and Ajit Prakash</i>	
2.1	Introduction	43
2.2	Chemistry and biosynthesis of nicotinamide adenine dinucleotide	46
2.3	Nicotinamide adenine dinucleotide-dependent enzymatic systems	50
2.4	Physiological and molecular significance of nicotinamide adenine dinucleotide	51
2.5	Nicotinamide adenine dinucleotide precursors: nicotinamide mononucleotide and nicotinamide riboside	52
2.6	Therapeutic potential and translational evidence	53
2.7	Analytical and experimental methods	55
2.8	Challenges and unresolved questions	56
2.9	Future directions and perspectives	58
2.10	Conclusions	60
	References	60
Part 2	Sirtuins and aging	
3.	Sirtuins in senescence, mitochondrial health, and longevity	65
	<i>Sanjib Manna, Purabi Das and Subhajit Mandal</i>	
3.1	Introduction	65
3.2	Sirtuins in cellular senescence	67
3.3	Sirtuins and mitochondrial health	72
3.4	Sirtuins and longevity	84
3.5	Therapeutic implications and future directions	87
3.6	Conclusion	89
	References	90

4.	DNA repair and genome maintenance via sirtuin pathways	99
	<i>Samarendra Singh, Farhan Raza, Aditya Raj, Gautam Singh and Navjot Kaur Sandhu</i>	
4.1	Introduction	99
4.2	Sirtuins in DNA repair pathways	104
4.3	Chromatin dynamics and DNA damage response	113
4.4	Nicotinamide adenine dinucleotide availability and metabolic regulation	118
4.5	Pathological implications of sirtuin dysfunction	121
4.6	Therapeutic potential of targeting sirtuins	125
4.7	Future perspectives	129
4.8	Conclusion	131
	References	132
Part 3	Sirtuins in metabolic regulation	
5.	Sirtuins and energy homeostasis	141
	<i>Bhupender Nehra, Rishabh Kasnia, Sunaina Demiwal, Sourabh Suthar and Biplab Debnath</i>	
5.1	Introduction	141
5.2	Molecular mechanisms linked to sirtuin action	145
5.3	Sirtuins and cellular energy homeostasis	147
5.4	Tissue-specific roles of sirtuins in metabolic regulation	150
5.5	Sirtuins and nutrient sensing pathways	154
5.6	Sirtuins in metabolic disorders	155
5.7	Sirtuins and cellular stress responses	158
5.8	Pharmacological modulation of sirtuins	160
5.9	Sirtuins, aging, and longevity	165
5.10	Emerging insights and omics approaches	168
5.11	Therapeutic implications and translational perspectives	169
5.12	Future directions	171

5.13	Conclusions	171
	References	172
6.	Role of sirtuins in glucose and lipid metabolism	183
	<i>Verma Swastik and Kotnis Ashwin</i>	
6.1	Introduction	183
6.2	Overview of sirtuins	184
6.3	Nicotinamide adenine dinucleotide metabolism and mechanism of action	186
6.4	Regulation of sirtuin expression and activity	188
6.5	Carbohydrate-specific roles	190
6.6	Lipid-specific roles of sirtuins	192
6.7	Integrated carbohydrate–lipid regulation	194
6.8	Sirtuins in disease and physiology	197
6.9	Therapeutic targeting	199
6.10	Experimental approaches and methods	202
6.11	Conclusions and future directions	205
	References	205
7.	Sirtuins in caloric restriction and fasting responses	215
	<i>Rizwan Ahamad, Nazreen Tabassum, Nasr Ali Emad, Mohd Aqil and Mohd Mujeeb</i>	
7.1	Introduction	215
7.2	Classification and functions of sirtuins	216
7.3	Roles of SIRT1	218
7.4	Modulation of SIRT1	219
7.5	Other members of the sirtuins family	220
7.6	Adenosine monophosphate-activated protein kinase	222
7.7	Sirtuin activation in caloric restriction and fasting	224
7.8	Functional roles in metabolic adaptation	227
7.9	Sirtuins in aging and disease prevention	235

7.10	Therapeutic potential and future perspectives	238
	References	239
Part 4	Sirtuins in disease pathology	
8.	Sirtuins in neurodegenerative diseases	249
	<i>Neetu Sachan, Zeeshan Ali, Nishat Fatma and Phool Chandra</i>	
8.1	Introduction	249
8.2	Functional roles of individual sirtuins	251
8.3	Mechanisms of sirtuin action in the nervous system	254
8.4	Sirtuins in major neurodegenerative diseases	262
8.5	Pharmacological activators	268
8.6	Sirtuin inhibitors and dual modulators	269
8.7	Experimental and clinical evidence	274
8.8	Clinical and translational perspectives	276
8.9	Translational challenges and limitations	279
8.10	Conclusion	280
	References	281
9.	Sirtuins in cardiovascular health	291
	<i>Anas Islam, Badruddeen, Mohammad Irfan Khan, Juber Akhtar and Asad Ahmad</i>	
9.1	Introduction	291
9.2	Expression and localization of sirtuins in cardiovascular tissues	293
9.3	Mechanistic roles of sirtuins in cardiovascular physiology	297
9.4	Sirtuins in specific cardiovascular diseases	300
9.5	Sirtuin modulators: therapeutic potential in cardiovascular disease	304
9.6	Sirtuins and cardiometabolic syndrome	309
9.7	Crosstalk with other cardioprotective pathways	312

9.8	Challenges and future directions	316
9.9	Conclusion	318
	AI disclosure	319
	References	319
10.	The role of sirtuins in cancer progression	331
	<i>Anas Islam, Usama Ahmad, Mohd Muazzam Khan and Talib Hussain</i>	
10.1	Introduction	331
10.2	Mechanistic pathways regulated by sirtuins	334
10.3	Functional roles of sirtuins in cancer	337
10.4	Sirtuins in cancer metabolic reprogramming	341
10.5	Therapeutic targeting strategies	345
10.6	Future perspectives in personalized cancer therapy	351
10.7	Conclusion	355
	AI disclosure	355
	References	356
11.	Sirtuins in inflammation and autoimmunity	363
	<i>Mirunalini Gobinath, Parikshit Roychowdhury, Sagarika Mukherjee and Mohd Aftab Siddiqui</i>	
11.1	Introduction	363
	References	382
Part 5	Therapeutic applications	
12.	Sirtuin modulators: small molecules and natural compounds	393
	<i>Rupal Dubey and Pranav Kumar Prabhakar</i>	
12.1	Introduction	393
12.2	Enzymatic activity of sirtuins	395
12.3	Small-molecule modulators of sirtuins: an overview	397

12.4	Future perspectives	402
12.5	Conclusion	403
	References	404
13.	Sirtuin-targeted therapies: current challenges, clinical trials, and future directions	409
	<i>Binapani Barik, Lipanjali Badhei and Martin F. Desimone</i>	
	List of abbreviations	409
13.1	Introduction	410
13.2	Introduction to targeted therapy	411
13.3	Limitations of targeted therapy	411
13.4	Importance of targeting cellular regulators	412
13.5	Sirtuins: model of cellular regulation therapy	414
13.6	Sirtuins	415
13.7	Structure of sirtuin	415
13.8	Member of sirtuin family	416
13.9	General and biological function of sirtuin	417
13.10	Targeted therapies	419
13.11	Drawbacks of conventional drug therapy	420
13.12	Potential of sirtuins as a targeted therapy	421
13.13	Current challenges in sirtuin-targeted therapies	423
13.14	Clinical trials	430
13.15	Future direction	432
13.16	Conclusion	434
	References	434
14.	Translational perspectives in drug discovery	441
	<i>Arpita Robel Khamle, Varshini Dayanand Kore, Abhishek Lakhera, Saroj Kumar Panda, Manish Bhalla and Parth Sarthi Sen Gupta</i>	
14.1	Introduction	441
14.2	Sirtuins as therapeutic targets	446

14.3	Translational drug discovery pipeline for sirtuins	449
14.4	Strategies to modulate sirtuin activity	454
14.5	Technological advancements	459
14.6	Challenges and limitations	462
14.7	Translational evaluation of sirtuin modulators	464
14.8	Emerging and future directions	466
14.9	Conclusion	468
	References	470
Part 6	Future directions and challenges	
15.	Emerging trends in sirtuin research	481
	<i>Shubhadeep Mondal, Suratna Dass, Raju Samanta, Biplab Debnath, Mohini Mondal and Bimlesh Kumar</i>	
15.1	Introduction	481
15.2	The sirtuin family: structure and isoforms	485
15.3	Sirtuins and their role in cellular homeostasis	489
15.4	Sirtuins in DNA repair and genome stability	492
15.5	Mitochondrial function and sirtuins	496
15.6	Sirtuins in immune response modulation	498
15.7	Advancements in sirtuin substrate discovery	502
15.8	Sirtuin modulation and therapeutic potential	506
15.9	Isoform-specificity and clinical implications	511
15.10	Ongoing controversies and future directions	514
15.11	Conclusion	519
	References	521
16.	Technological advancements in sirtuin analysis	529
	<i>Amlan Bishal, Nabanita Manna, Bratati Pakhira, Sudeshna Khanra and Debjita Sett</i>	
16.1	Introduction	529
16.2	Conventional methods for sirtuin analysis	532

16.3	High-throughput screening techniques	535
16.4	Structural and biophysical analysis	537
16.5	Omics-based approaches	540
16.6	Advanced imaging and live-cell analysis	543
16.7	Computational and systems biology tools	546
16.8	Emerging nanotechnology and microfluidic platforms	548
16.9	Challenges, limitations, and future directions	551
16.10	Conclusion	552
	Acknowledgements	552
	Credit author statement	552
	Conflict of interest	553
	Ethical statement	553
	References	553
17.	Experimental tools for sirtuin modulation: from CRISPR to chemical biology	563
	<i>Vijay Singh, Aniruddha Sen, Biplab Debnath, Radheshyam Pal and Mohini Mondal</i>	
17.1	Introduction	563
17.2	Molecular basis of sirtuin function	564
17.3	Genetic tools for sirtuin modulation	568
17.4	High-throughput screening for modulators	569
17.5	Biochemical and biophysical assays	574
17.6	Synthetic biology and protein engineering tool	575
17.7	Metabolic engineering and cofactor modulation	576
17.8	Translational applications	580
17.9	Challenges and future directions	583
17.10	Conclusion	586
	References	588

18. Ethical and clinical implications of sirtuin therapies	597
<i>Meenakshi Attri, Mohit Agrawal, Asha Raghav, Samiksha Mishra, Hema Chaudhary, Manmohan Singhal and Narender Yadav</i>	
18.1 Introduction	597
18.2 Clinical considerations	598
18.3 Ethical implications	603
18.4 Regulatory and policy considerations	605
18.5 Future perspective	606
References	607
Author index	611
Subject index	631

Sirtuins in inflammation and autoimmunity

Mirunalini Gobinath¹, Parikshit Roychowdhury², Sagarika Mukherjee¹,
Mohd Aftab Siddiqui³

¹DEPARTMENT OF PHARMACOGNOSY AND PHYTOPHARMACY, JSS COLLEGE OF PHARMACY, JSS ACADEMY OF HIGHER EDUCATION AND RESEARCH, OOTY, TAMIL NADU, INDIA ²DEPARTMENT OF PHARMACEUTICS, JSS COLLEGE OF PHARMACY, JSS ACADEMY OF HIGHER EDUCATION AND RESEARCH, OOTY, TAMIL NADU, INDIA ³FACULTY OF PHARMACY, INTEGRAL UNIVERSITY, LUCKNOW, UTTAR PRADESH, INDIA

11.1 Introduction

Sirtuins are nicotinamide adenine dinucleotide (NAD⁺)-dependent enzyme that plays a key role in various biological and metabolic processes. They also act as energy sensors, correlate with NAD⁺ cofactor, and perform crucial activities in intracellular energetics (Finkel et al., 2009). In earlier research, scientists have highlighted that sirtuins have a crucial role in lifespan regulation (especially in lower organisms), caloric restriction, and act as broad regulators of cellular physiology and longevity. In addition, sirtuins have major functions in higher organisms, especially mammals, which regulate cellular stress resistance, energy metabolism, genomic stability, epigenetics, cancer biology, and many more. This has motivated researchers in recent decades to discover the role of sirtuins in several diseases and health (Wu et al., 2022).

Sirtuins are also classified as histone deacetylases (HDACs) class III and require NAD⁺ as a cosubstrate for their catalytic mechanism, while HDACs remove acetyl groups on histone and nonhistone proteins of lysine residues (Jin et al., 2024). This encompasses activities such as DNA damage repair, mitochondrial homeostasis, several types of apoptosis mechanisms, autophagy, and inflammatory and immune pathways. This is the reason why it connects with the pathogenesis of various age-related chronic inflammatory disorders (Wątroba et al., 2017). Formerly, sirtuins were classified as silent information regulator 2 (Sir2) proteins, which were discovered in yeast species (*Saccharomyces cerevisiae*) as a gene silencing factor that increases longevity. Later, it was discovered in *Drosophila melanogaster* and *Caenorhabditis elegans*. Sir2 depends mainly on NAD⁺ and acts on histones as a deacetylase, with the enzyme mono-ADP-ribosyltransferase. Later, the role of NAD-dependent deacetylation in calorie restriction/starvation and ageing was associated with several species, which highlighted many researchers to correlate the role of sirtuins in cellular senescence and age-related disorders (Sebastián, Satterstrom, et al., 2012).

The sirtuin family consists of seven homolog members, from SIRT1 to SIRT7, which are present in subcellular localization in mammalian cells and allow them to regulate cellular metabolic processes (Table 11-1). Some are distributed in both cytoplasmic and nuclear localizations; for example, SIRT1 plays a role in autophagy, apoptosis, oncogenesis, and differentiation of cells. SIRT2 is located to a large extent in the cytoplasm, where it functions in α -tubulin deacetylation, and also translocates between the cytoplasm and the nucleus to assist as a checkpoint protein in mitosis (North et al., 2003). When all SIRT family members have deacetylase activity, some of them, like SIRT 4 and 6, have mono-ADP-ribosyltransferase activity. SIRT 3–5 are distributed in mitochondria and have different enzymatic activities like NAD-dependent desuccinylase, demalonylase, and weak deacetylase action, whereas SIRT 6 is in the nucleus, which is a chromatin-associated nuclear protein with poor deacetylase activity, and SIRT 7 in the nucleolus with deacetylase action (Grootaert & Bennett, 2022).

Structurally, sirtuins are distinguished from other zinc-dependent classical HDACs, such as classes I, II, and IV. The uniqueness of sirtuins is that they depend on the stoichiometric cosubstrate, NAD⁺, for deacetylase activities, whereas traditional HDACs are dependent on zinc ion-water catalytic mechanisms. Subsequently, the dependency on NAD⁺ in sirtuins has established a direct link between cellular energy metabolism, bioenergetics, and epigenetics. This is due to the role of NAD⁺ as a cofactor in various biochemical processes (glycolysis, oxidative phosphorylation, TCA cycle) and redox reactions (Katsyuba et al., 2020). In the perspective of chemical biology, apart from deacetylase properties, sirtuins also perform deacylase activity, which modifies acyl groups, enabling them to regulate posttranslational modifications. In addition to catalytic regions, which are a conserved core region, C and N terminal regions are located in sirtuins, which differ in chemical composition, length, and sensitivity to posttranslational modifications, and change the binding site in some sirtuin families (B. Chen et al., 2015).

Autoimmune disorders are a group of conditions that generate autoantibodies and attack specific cells or tissues, mistaking them as a foreign substance. The link between inflammation and autoimmunity also connects with sirtuins, as they play a major role in innate and adaptive immune responses. Thus this chapter comprehensively explains the role of sirtuins in inflammatory signaling pathways, autoimmune responses, and various aspects of immunology and sirtuin biology. Thus understanding more about sirtuins at the cellular and molecular levels could assist in correlating with health and disease pathology.

11.1.1 Cellular and molecular biology of sirtuins in inflammation and autoimmunity

Inflammation is a foundational biological response to stimuli such as cellular injury, tissue damage, or invasion of pathogens. These events cause recruitment of immune cells like inflammatory mediators, cytokines, interleukins, neutrophils, macrophages, etc., and initiate tissue repair mechanisms. Inflammation occurs in two phases, that is, acute and chronic; however, improper regulation of these inflammatory pathways could lead to chronic inflammation and persistent illness. The link between sirtuins and inflammation is crucial