Naunyn-Schmiedeberg's Archives of Pharmacology
https://doi.org/10.1007/s00210-024-03263-9

REVIEW

Sirtuin insights: bridging the gap between cellular processes and therapeutic applications

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Received: 19 March 2024 / Accepted: 24 June 2024

Abstract

The greatest challenges that organisms face today are effective responses or detection of life-threatening environmental changes due to an obvious semblance of stress and metabolic fluctuations. These are associated with different pathological conditions among which cancer is most important. Sirtuins (SIRTs; NAD^+-dependent enzymes) are versatile enzymes with diverse substrate preferences, cellular locations, crucial for cellular processes and pathological conditions. This article describes in detail the distinct roles of SIRT isoforms, unveiling their potential as either cancer promoters or suppressors and also explores how both natural and synthetic compounds influence the SIRT function, indicating promise for therapeutic applications. We also discussed the inhibitors/activators tailored to specific SIRTs, holding potential for diseases lacking effective treatments. It may uncover the lesser-studied SIRT isoforms (e.g., SIRT6, SIRT7) and their unique functions. This article also offers a comprehensive overview of SIRTs, linking them to a spectrum of diseases and highlighting their potential for targeted therapies, combination approaches, disease management, and personalized medicine. We aim to contribute to a transformative era in healthcare and innovative treatments by unraveling the intricate functions of SIRTs.

Keywords Sirtuins · Cancer promoters or suppressor · Therapeutic intervention · Disease management

Introduction

Silent information regulator 2 (SIR2) is highly conserved across both prokaryotes and eukaryotes (Frye 2000; Brenner 2022). It was initially discovered for its remarkable ability to extend the lifespan of yeast cells, subsequently associating it with longevity regulation (Zhang et al. 2020a). The eukaryotic counterparts of SIR2, known as sirtuins (SIRTs), have garnered increasing fascination due to their dual role in cancer. These enzymes are bifunctional, exhibiting both oncogenic/promoting and tumor-suppressing functions across various types of cancers. Given that cancer cells heavily depend on mitochondrial cell signaling for their proliferation, development, and the disruption of metabolic pathways leading to heightened the mitochondrial apoptosis becomes a significant factor (George and Ahmad 2016). The American Cancer Society has predicted a concerning trend, projecting that the incidence of cancer cases in the USA will double by 2030, resulting in a total of 21.4 million cases and 13.2 million deaths (Siegel et al. 2015).

Shin-ichiro Imai and collaborators' discovery of SIRTs as NAD + -dependent protein deacetylases kindled interest in NAD^+ metabolism (Imai et al. 2000). Through phylogenetic analysis of core domains from various prokaryotes and eukaryotes, mammalian SIRTs can be categorized into four distinct classes: class-I (SIRT1-SIRT3), class-II (SIRT4), class-III (SIRT5), and class-IV (SIRT6 and SIRT7). While SIRT1 is nuclear, SIRT2 localizes in the cytoplasm (Table 1) and is located on separate chromosomes. Notably, SIRT2 dynamically shuttles between the cytoplasm and nucleus (George and Ahmad 2016). Among the trio of SIRTs—SIRT3, SIRT4, and SIRT5—SIRT3 stands out prominently for its significant role in repressing the progression of

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Published online: 08 July 2024

Table 1 Structural properties and location of sirtuins on different chromosomes

Sr. no	Property	SIRT1	SIRT2	SIRT3	SIRT4	SIRT5	SIRT6	SIRT7	Ref
1	Amino acid number	747	389	399	314	310	355	400	(Jaiswal et al. 2022)
2	Mitochondrial sequence length	Deficient	Deficient	24	1–28	1–36	Deficient	Deficient	(Villalba and Alcaín, 2012)
3	Active site position	363	187	248	161	158	133	187	(Voelter-Mahlknecht and Mahlknecht 2006)
4	Binding sites	6	6	5	6	8	6	6	(Voelter-Mahlknecht et al. 2005)
5	Nucleotide binding sequence	4	5	4	4	4	4	4	(Mahlknecht et al. 2006)
6	Co-factor	Zn^{2+}	Zn^{2+}	Zn^{2+}	Zn^{2+}	Zn^{2+}	Zn^{2+}	Zn^{2+}	
7	Mutagenesis region	16	23	7	1	4	1	4	
8	SIRT domain length (amino acids)	255	276	257	270	269	240	242	
9	Presence on chromosome	10	19	11	12	6	19	17	
10	Exons	9	16	7	4	10	8	10	
11	Location within cell	Cytoplasm, nucleus	Cell membrane, chromosome, cytoplasm, cytoskeleton, microtubule, nucleus	Mitochondrial matrix, nucleus, cytosol	Mitochondrial matrix, nucleus, cytosol	Mitochondria, Cytosol, small amount in the nucleus	Nucleus, nucleoplasm, chromosome, cytoplasm	Nucleus, cytoplasm, chromosome, chromatin	
12	α-Helix	8	8	17	11	15, 14, 9	8	Lack	(North and Verdin 2004)
13	β-Strand	6	6	9	9	11, 9	9	Lack	(Davenport et al. 2014) (Pan et al. 2011)
14	Crystal structure resolution	3.20 Å	1.70 Å	2.0Å (4BV3)	2.0Å (4BV3)	2.0Å (4BV3)	2.00 Å	2.33 Å	(Singh et al. 2018)
15	Cofactor binding site				Cys169, Cys172, Cys220, and Cys223	Cys166, Cys169, Cys207, and Cys212			(Sanders et al. 2010)
16	Histone substrates	H3, H4, H1	H3, H4,	H3, H4,			H3	H3	(Martínez-Redondo and Vaquero 2013)

Table 1 (continued)

Sr. no	Property	SIRT1	SIRT2	SIRT3	SIRT4	SIRT5	SIRT6	SIRT7	Ref
17	Non-histone substrates	BCL6, p53, DNMT1, Ku70, Tip60, Tqt, P300,AceCS1, HMGCS1	$NF_{\chi}B$, α-tubulin, p53, PEPCK1, FoxO3a	MnSOD, AceCS2, IDH2, HMGCS2, LCAD, GD	GD, MCD	CPS1	TNFα, CtIP	GABPβ1, p53	(Fiorino et al. 2014)
18	K_{cat}/K_M	SIRT1-CC 67,700 M^{-1} min^{-1} SIRT1-N-CC 653,000 M^{-1} min^{-1} for p53(372–389) K382Ac	3.5×10^{-1} M^{-1} S^{-1} for deacetylation	5.40×10^{2} S^{-1} M^{-1} for delactylation (H4K16 peptide)	0.083 ± 0.004 S^{-1} M^{-1} for H3(4–13) K9Acetyl peptide	18,699 $M^{-1}S^{-1}$ for deglutarylation, 13,995 $M^{-1}S^{-1}$ desuccinylation, 3758 $M^{-1}S^{-1}$ demalonylation, 16 $M^{-1}s^{-1}$ deacetylation	Deacetylion 157.89 ± 21.86 L/mol.s; for NAD^+ 882.62 ± 114.25 L/mol.s	Km = 253 ± 25 μM, kcat = 3.6 ± 0.15 min^{-1} for H3K18Ac deacetylation	(Pan et al. 2012; Roessler et al. 2014; Fan et al. 2018; Li et al. 2018; Mitra and Dey 2020)

various age-related pathologies, including tumorigenesis, hearing impairments, and cardiac muscle fibrosis (Lombard et al. 2011). These SIRTs are also intricately involved in energy regulation and metabolic processes that are notably impaired in cardiac issues. Consequently, they emerge as pivotal contributors to various heart-related conditions such as myocardial ischemia–reperfusion injury and heart failure (Bugger et al. 2016). SIRTs play diverse roles in cancer initiation and progression by influencing cellular responses to genomic instability. They thereby regulate DNA repair, cell cycle progression, apoptosis, and cell survival, while also modulating tumor-associated metabolism and molding the tumor microenvironment (Bosch-Presegué and Vaquero 2011). Additionally, SIRTs introduce novel modes of mitochondrial regulation, including ADP-ribosylation (Hopp et al. 2021), lysine acetylation (Lombard et al. 2007), succinylation (Alleyn et al. 2018), malonylation (Peng et al. 2011), and glutarylation (Tan et al. 2014), which are altered by SIRTs.

In the preceding review, we subsequently delve into the recent advancements, revealing distinct mechanisms by which individual SIRTs (SIRT1–7) influence diverse cancer-related and metabolic pathways. Our exploration extends to considering activators and inhibitors as potential strategies against different cancer forms. By examining their functions and interactions across contexts, the study aimed to uncover therapeutic approaches targeting SIRT pathways. Additionally, the investigation probed the modulation of SIRT activities via natural or synthetic molecules, illuminating drug development possibilities. This study sought a deeper grasp of SIRT biology and its potential as therapeutic targets, aiming to enhance disease management and patient outcomes.

Structural composition of SIRTs

SIRTs constitute a highly conserved enzyme family (Table 1) spanning across species from bacteria to humans, governing pivotal physiological processes such as metabolic homeostasis, DNA repair, and longevity (Pannek 2018). Their deacetylase activity targets numerous acetylated lysine residues on proteins, including transcription factors. The disruption of post-translational modifications due to mitochondrial dysfunction can contribute to a range of disorders, including cancer (Sorrentino et al. 2018). While the mitochondrial leader sequences of various pre-proteins differ significantly in terms of amino acid sequence, they all share the common function of directing proteins to the mitochondria (Hammen and Weiner 1998). SIRT3 exists in multiple isoforms, yet only the mitochondria house the functionally active full-length isoform SIRT3 predominantly resides within the mitochondrial matrix, cytosol, and also the nucleus (Jaiswal et al. 2021). The protein boasts five binding sites,

out of which four are meant for metallic binding—acting as zinc cofactors—and four are allocated for nucleotide binding regions (Table 1). The active site is situated at position 248. Functioning as a class III histone deacetylase, SIRT3 operates independently of zinc (Seto and Yoshida 2014). Its domain stretches over 257 amino acids, encompassing seven mutagenesis regions, 17 α-helices, and nine β-strands that give rise to β-sheets (Sanders et al. 2010). The metallic binding sites are associated with cysteine residues, playing a crucial role in retaining the Zn^{2+} ions and upholding the stability of the minor domain. These interacting sites are located at Cys256, Cys259, Cys280, and Cys283. The functionality of SIRT4's lipoamidase remains unchanged from bacteria to humans, underscoring the significance of lipoic acid as a metabolic cofactor (Rowland et al. 2017). Meanwhile, SIRT5 is tasked with eliminating negatively charged lysine oscillations through the addition of a glutaryl group, succinyl, acetyl, malonyl, and crotonyl moieties (Tan et al. 2014).

Cross talk of SIRTs with cancer

The pivotal connection between SIRTs and cancer emerged when SIRT1 deacetylates repressed the activity of p53, a prominent tumor suppressor. The significance of mitochondrial SIRTs in cancer is not surprising, given that cancer's inception and progression entail substantial alterations in cellular metabolism and mitochondrial energetics (Fig. 1). Cancer cells display heightened metabolic activity, consuming more metabolic energy than healthy cells (Cantor and Sabatini 2012). Furthermore, recent findings elucidate that fidelity proteins or mitochondrial anti-aging proteins, such as SIRT3 and SIRT4, respond to shifts in cellular nutrient conditions adjusting enzyme activities toward specific downstream targets, harmonizing energy generation with available energy and ATP utilization (Zhu et al. 2014). Mitochondrial dysfunction disrupts redox equilibrium and metabolic pathways, hastening the aging process and contributing to metabolic disorders like type 2 diabetes and insulin resistance (Wang and Wei 2020; Salekeen et al. 2021). The repertoire of SIRTs often functions as tumor suppressors, exemplifying their multifaceted roles (Table 2).

Cui and co-researchers uncovered that SIRT3 overexpression amplifies lactate production, ATP synthesis, and glycolysis which in turn augments manganese superoxide dismutase (MnSOD) activity, leading to reduced ROS levels and fostering the growth of gastric cancer cells (Cui et al. 2015). FOXO1-mediated induction of autophagy holds pivotal significance for its role as a tumor suppressor (Zhao et al. 2010). SIRT3 also partakes in deacetylating lysine residues in FOXO3, a process crucial for managing mitochondrial functions such as mitochondrial fission or fusion processes, mitophagy, and mitochondrial biogenesis (Tseng et al. 2013). Deacetylation of ECHS1 by SIRT3, surprisingly revealed that knocking down ECHS1 under nutrient-rich conditions led to a buildup of cytoplasmic fatty acid accumulation in Chang cells and HEK293 cells, mirroring acetylated ECHS1 (Zhang et al. 2017a). SIRT3 overexpression bolstered the expression of mitochondrial transcription factor A (TFAM) while significantly diminishing protein acetylation at K154 facilitating the tumor-permissive phenotype in human renal carcinoma-derived 786-O cell line, (Liu et al. 2018a). The deacetylation activity of SIRT3 leads to the deactivation of SKP2, rendering it an attractive target for cancer treatment. The acetyltransferase p300 catalyzes

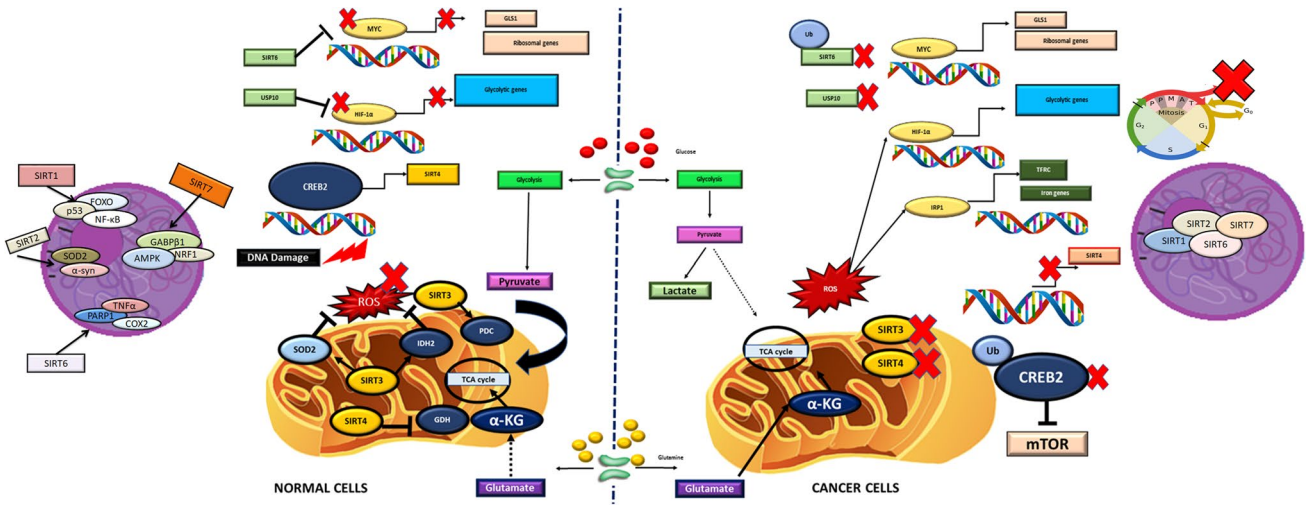


Fig. 1 Role of different sirtuins in the regulation. SIRTs are involved in a series of malignancies that can be compared with normal cells. SIRTs can act as promotors as well as inhibitors which is presented by the Red Cross

Table 2 Role of sirtuins in different metabolic disorders

Type of SIRTs	Activity	Substrate	Mechanism	Function	Ref
SIRT1	Deacetylation	NF-κB	S-nitrosation of SIRT1 increases deacetylation of the substrate and cellular targets	Metabolism and aging	(Yeung et al. 2004)
	Activation	Resveratrol	Activation due to covalently attached fluorophore	Cell cycle regulation, life span extension	(Chao et al. 2017)
	Activation	p53W	Activation through the allosteric mechanism and conformational changes in NTD	Prevents cell senescence	(Borra et al. 2005)
	Deacetylation	p65	Enhanced deacetylation of p65 causes a reduction in TNFα secretion	Reduction in inflammation	(Yang et al. 2012)
	Deacetylation	NFAT	NHR and RHR of NFAT mediated with SIRT1 and deacetylated NFATc3	Reduces inflammation	(Jia et al. 2014)
	Activation	FOXO1	Activation of gene transcriptional and basal activity of MRP2 cause an increase in TAMR-MCF-7 cells inhibits expression of the substrate and enhances the cytotoxic effect	Prevents cell senescence	(Xia et al. 2013)
	Deacetylation	AP-1	Deacetylation of activator protein-1 to suppress transcriptional activity	Reduces inflammation	(Zhang and Kraus 2010)
SIRT2	Deacetylation	αTubulin	Deacetylases Lys-40 both in vitro and in vivo	Cytoskeleton modulation	(Skoge et al. 2014)
	Deacetylation	Histone H3	Deacetylation of H4K16Ac for condensed chromatin	Cell cycle regulation	(Vaquero et al. 2006)
	Deacetylation	*p*300	Deacetylation of a lysine residue and binding to the PIC. It undergoes autoacetylation and deacetylation	Regulation of p300 autoacetylation	(Black et al. 2008)
	Activation	HOXA10	Acts as a binding partner by interacting with the homeobox transcription factor	Not known	(Bae et al. 2004)
	Phosphorylation	CDK1, cyclin E–Cdk2	Phosphorylation of Ser-331 inhibits the catalytic activity	Inhibition of SIRT2 catalytic activity	(Pandithage et al. 2008)
	Deacetylation	Par-3	Deacetylation of Par-3 lowers the activity of polarity complex signaling component aPKC and regulates myelin formation	Modulation of peripheral myelination	(de Oliveira et al. 2012)

Table 2 (continued)

Type of SIRTs	Activity	Substrate	Mechanism	Function	Ref
SIRT3	Activation	AceCS2	Production of acetyl-CoA from acetate	Metabolism, ATP synthesis	(Hallows et al. 2008)
	Activation	IDH2	Production of α-ketoglutarate for TCA cycle from isocitrate	Metabolism, overexpression cause tumorigenesis	(Lu et al. 2017)
	Activation	GDH	Production of α-ketoglutarate from glutamate	Metabolism, energy generation	(Schlicker et al. 2008)
	Activation	MPC1	SIRT3 binds and activated the MPC1	The poor prognosis of many cancers	(Yang et al. 2015a)
	Activation	PDH	PDH Convert pyruvate to acetyl-CoA	Metabolism, energy production, increased activity in cancer	(Ozden et al. 2014)
	Activation	PDP1	Phosphorylation of PDP1 at Tyr381 increases the separation of SIRT3 from PDH	Activation of PDH	(Wang et al. 2014)
	Activation	MnSOD	Deacetylation of lysine residue directs MnSOD activity	Tumor suppression, detoxification of ROS, and play role in oxidative stress	(Tao et al. 2010)
	Activation	OGG1	Deacetylation activates the OGG1	DNA repairing inhibits apoptosis thus it promotes tumorigenesis	(Zhang et al. 2013)
	Deactivation	GOT2	Deacetylation of GOT2 inactivates the malate-aspartate shuttle	Suppress the tumor growth in pancreatic cancer, low energy production	(Yang et al. 2015a)
	Activation	LDHA	Deacetylation LDHA activates it	Promotes glycolysis and proliferation in cancer cells by participating in anaerobic glycolysis	(Cui et al. 2015)
	Activation	FOXO1	Deacetylation of FOXO1 activates it	Enhancing the ubiquitin ligase activity and improving autophagy flux	(Li et al. 2016)
	Activation	FoxO3a	Deacetylation of lysine residue activates FoxO3a	Minimize aging, decrease ROS level	(Zeng et al. 2016)
	Activation	MDH_2	Deacetylation of lysine residue activates it	Regulate malate aspartate shuttle	(Rardin et al. 2013)
	Activation	ECHS1	Deacetylation of ECHS1 activate it	Oxidation of fatty acids, signaling, and apoptosis	(Zhang et al. 2017b)
	Activation	TFAM	Overexpression enhances the activity of TFAM	Mitochondrial biogenesis	(Liu et al. 2018b)
	Activation	LON	Deacetylation activates its enzymatical activity	Mitochondrial homeostasis, decomposing damaged protein	(Gibellini et al. 2014)
	Deactivation	SKP-2	Deacetylation at p300 to inactivate SKP-2	Deacetylation of SKP-2 help in cancer treatment	(Liu et al. 2020)
	Deactivation	BAG-2	SIRT3 and BAG-2 act on p-53	Inhibiting the activity of p53 in different cancers. Mainly bladder carcinoma	(Michán et al. 2010)

Table 2 (continued)

Type of SIRTs	Activity	Substrate	Mechanism	Function	Ref
SIRT4	ADP-ribosyltransferase	GDH	Repress glutamine metabolism in Kreb's cycle Inhibition of TCA cycle	Suppress tumorigenesis, an active component in response to DNA damage mechanism	(Jeong et al. 2013a)
	Deacetylation	MCD	Inhibit malonyl CoA-decarboxylase	Suppress fatty acid oxidation	(Tomaselli et al. 2020)
SIRT5	Deacetylation	CPS1	SIRT5 deacetylates CPS1 and upregulates its activity	Ammonia detoxification and urea cycle	(Nakagawa and Guarente 2011)
	Desuccinylates	GLS2	Inhibition of GLS2 by reducing glutamate and ammonia	Suppress tumorigenesis. Reduced expression of autophagy and mitophagy	(Yang et al. 2017)
SIRT6	Deactivation	PARP1	Knockdown SIRT6 inhibited HMGB1 cytoplasmic translocation and autophagy	Chemotherapeutic drug resistance	(Bajrami et al. 2021)
	Repression	KAP1	Blockage of KAP1-HP1α binding	Aging	(Van Meter et al. 2014)
	Activation	BAF170	Activation of a subset of NRF2 gene, SIRT6-mediated transcriptional activation	Chromatin formation	(Rezazadeh et al. 2019)
	Repression	HIF1α	Upregulation of glycolysis and diminished mitochondrial respiration	Cell survival, cancer, aging	(Kleszcz and Baer-Dubowska 2021)
SIRT7	Deacetylation	PAF53	DNA binding and enhanced pre-RNA synthesis	Cell cycle progression, biogenesis	(Chen et al. 2013) (Black et al. 2008)
	Hyperacetylation	PAF53	At lysine 373 by CBP, decreases rDNA occupancy	Regulation of cell proliferation	(Shin et al. 2013) (Chen et al. 2016)
	Deacetylation	U3–55 k	PCAF impairs associations	Ribosome biogenesis, coupling rDNA transcription, pre-rRNA processing	
	Deactivation	Myc	Repression of ribosomal protein expression, alleviation of ER stress	Lipid metabolism, hepatic homeostasis	
	Deacetylation	GABPβ1	Deacetylation of a central regulator of mitochondrial system	Cellular energy metabolism	
	Desuccinylation	H3K122	DNA double strands break in a PARP1-dependent manner and promote chromatin condensation and DSB repair	Cell survival	

acetylation at the first and second lysine sites (K68 and K71) within the SKP nuclear localization region, promotes SKP2 dimerization, and triggers the degradation of the downstream negative cell cycle regulator E-cadherin through the ubiquitination pathway in tumor tissues (Wang et al. 2012). Both SIRT3 and BAG2 collaborate in inactivating p53, leading to its degradation in cancers and inhibiting its activity. SIRT4 due to its regulatory control over glutamine metabolism act as a tumor suppressor (Jeong et al. 2013b). SIRT4 by repressing glutamine metabolism impeding the tricarboxylic acid cycle via ADP-ribosylation. Dual action of SIRT4 not only curtails tumorigenesis but also plays an active role in DNA damage response mechanisms (Jeong et al. 2013b). Beyond its involvement in tumorigenesis, SIRT4 also plays a role in other mitochondrial malfunction-related disorders such as insulin secretion, obesity, and cardiovascular diseases (Liu et al. 2013). SIRT5, possessing a phylogenetic connection to bacterial SIRTs, predominantly resides within the mitochondria with limited indications of extra-mitochondrial protein activity. However, the role of SIRT5 in cellular metabolism has been explored in a limited number of studies (Park et al. 2013), one notable function is the upregulation of CPS1 activity via its deacetylation. This elevation contributes to efficient ammonia detoxification and functioning of the urea cycle (Nakagawa et al. 2009). By desuccinylation, SIRT5 diminishes glutamate and ammonia levels, thereby inhibiting GLS2 and subsequently aiding in the suppression of tumorigenesis. This also leads to a reduction in the expression of autophagy and mitophagy (Polletta et al. 2015).

SIRTs and their impact on cancers

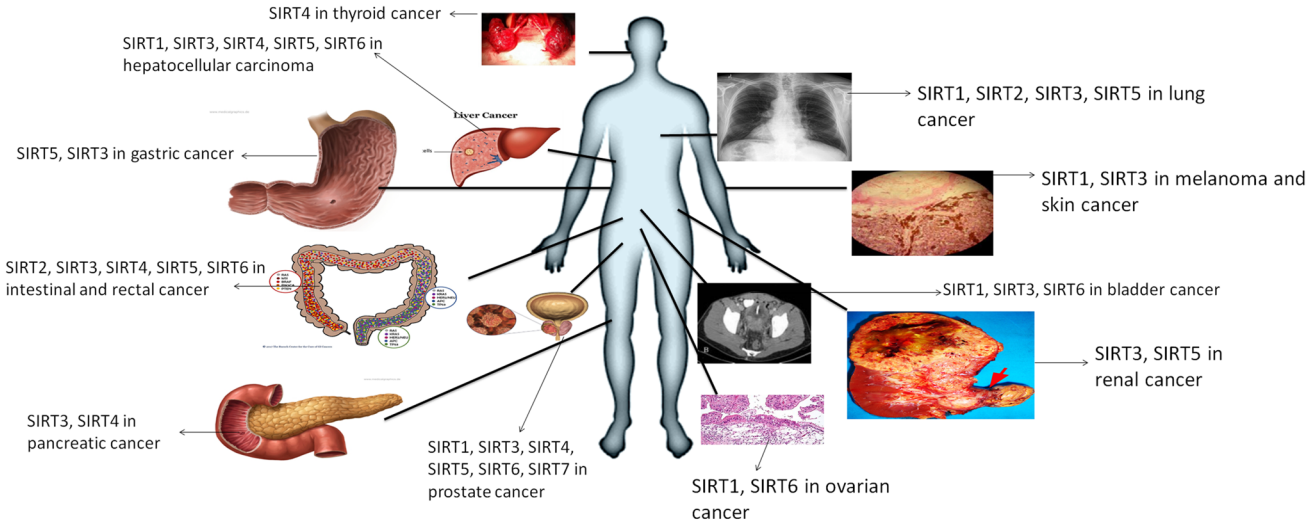
An array of solid evidence points toward SIRTs playing a pivotal role in orchestrating processes that often go awry in tumorous cells (Fig. 2). These processes encompass the regulation of chromatin structure, manipulation of the tumor microenvironment, maintenance of genomic stability, and the intricate orchestration of cellular metabolism. Consequently, the functions of SIRTs (SIRTS 1–7) exhibit a dichotomy: they might repress proliferation in certain cases while actively supporting it in others (Fig. 2). The details of these divergent roles are compiled in Table 3 and are explored comprehensively in the following sections.

Breast cancer

One of the most prevalent cancers in females is breast cancer (Sharma et al. 2010). Typically, BRCA1 acts as a transcription factor to maintain SIRT1 expression. This, in turn, inhibits acetylation at Lys9 (H3K9) of BRCA5, an anti-apoptotic gene, and represses its chromatin-level promoter activity. As a result, a direct link between the loss of BRCA1 function and the downregulation of SIRT1 has been established. The metastasis phase of breast cancer cells entails the downregulation of SIRT3, leading to the activation of ROS and SRC/FAK signaling, which in turn promotes metastasis (Lee et al. 2018). Conversely, SIRT3 overexpression suppresses ROS and SRC/FAK signaling, ultimately curbing tumorigenesis (Lee et al. 2018). Elevation of SIRT3 levels curtails cell growth and triggers oxidative phosphorylation in breast cancer cell lines (Pinterić et al. 2018). SIRT3's involvement extends to tamoxifen-resistant breast cancer cell lines (Zhang et al. 2013). Overexpressing PGC-1α and SIRT3 prompts apoptosis and impedes proliferation in MCF-7 cell lines. SIRT3 upregulation amplifies p21 expression and reduces ROS levels, inducing apoptosis in breast cancer (Xiao et al. 2013). The epithelial-mesenchymal transition, a hallmark of breast cancer, driven by oxidative phosphorylation and TGF/SMAD signaling, is notably influenced by SIRT3 deficiency. It leads to an upregulation of glycogen synthase kinase 3, thereby directly promoting TGF/SMAD signaling. This implies that SIRT3 could serve as a pivotal monitor of breast cancer progression (Hu et al. 2020). SF3B3 triggers autophagy in breast cancer tissues, while the small molecule activator of SIRT3, 1-methyl-benzyl amino amiodarone, induces apoptosis (Zhang et al. 2021). SIRT4 exhibits downregulation in breast cancer cells (Igci et al. 2016). Patients with low survival rates often demonstrate diminished SIRT4 levels in their tissues (Shi et al. 2016). In cases where CtBP increases GDH activity, this heightened metabolism suppresses SIRT4, thereby favoring tumor cell function (Wang et al. 2018a). SIRT4 is notably involved in glutaminolysis (Wang et al. 2018a). SIRT4 can initiate mitochondrial fusion, inhibiting both mitochondrial fission and mitophagy when denatured proteins become active. Consequently, stress-induced SIRT4 can impair mitochondrial quality control, resulting in mitochondrial malfunction (Lang and Piekorz 2017). SIRT4 enhances tamoxifen sensitivity in breast cancer by inhibiting the IL6-STAT3 pathway (Xing et al. 2019b). SIRT5 experiences upregulation in breast cancer. SIRT5's expression appears to counteract the activities of SIRT3 and SIRT4 in cell proliferation (Igci et al. 2016). Further investigation is needed to uncover the specific functions of SIRT5 in breast cancer.

Hepatocellular cancer

Liver cancer stands as the sixth most prevalent cancer worldwide. In this context, SIRT3, SIRT4, and SIRT5 undergo downregulation. Counterintuitively, overexpressing these SIRTs impedes cancer cell growth (Wang et al. 2014). Notably, SIRT3 overexpression curbs the PI3K/AKT pathway in hepatocellular carcinoma, leading to a subsequent inhibition of cell proliferation (Zeng et al. 2017). Elevated



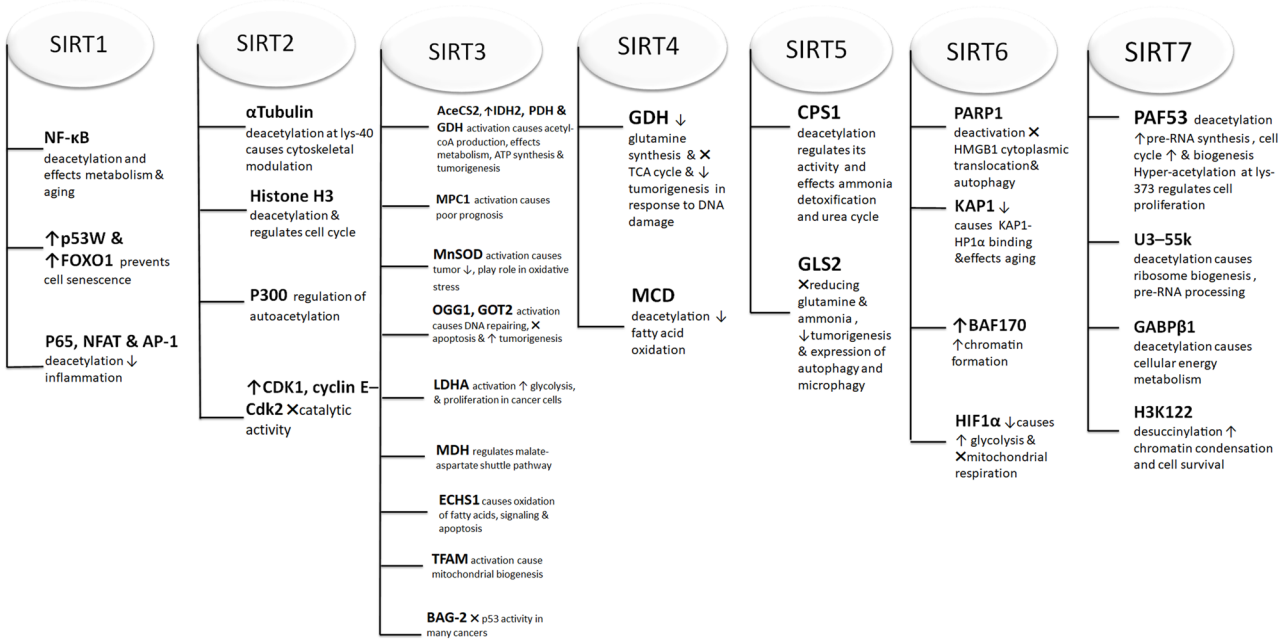


Fig. 2 Graphical representation of the role of sirtuins in different types of cancers along with their promoters and suppressors. SIRTs are involved in a series of cancerous growths including liver, gastric, pancreatic, colorectal, lung, thyroid, melanoma, and skin cancers

SIRT3 levels engender reduced proliferation and heightened apoptosis. This effect is manifested through BCL2-associated X (BAX), the tumor suppressor protein P53, and cell surface death receptors, all of which are essential for apoptosis (Liu et al. 2017). By deacetylating and activating glycogen synthase kinase 3, augmented SIRT3 levels instigate the pro-apoptotic protein BAX, ultimately promoting apoptosis (Song et al. 2016). SIRT3-mediated intracellular acidification activates BAX, thereby prompting apoptosis in hepatocellular carcinoma (Wang et al. 2018b). Additionally, SIRT3's role involves diminishing GSTP1, which in turn activates JNK activity in hepatocellular carcinoma (Tao et al. 2016). Elevated levels of histone methyltransferase deactivate kruppel-like factor 4 (KLF4), consequently inhibiting SIRT4. This inhibition leads to the promotion of aerobic glycolysis and the halt of oxidative phosphorylation, thereby fostering cancer cell proliferation (Chen et al. 2019a). The overexpression of SIRT4 curbs cancer cell development, and by interacting with the JAK2/STAT3 pathway, induces an aging phenotype. Elevated SIRT4 levels also boost the

Table 3 Metabolic role of sirtuins in different categories of cancers

Type of SIRT	Activity	Target	Regulation	Cancer	Ref
SIRT1 deacetylase	Suppressor	p53, p73, HIC1	↑ p35 acetylation induces cell arrest apoptosis and DNA repair and SIRT1 ↓ it. ↓ HIC1 ↑ SIRT1 and bypass apoptosis	Breast cancer, hepatic carcinoma, and some other types	(Lim 2006) (Lin and Fang 2013)
	Suppressor	FOXO1, FOXO3a, FOXO4, PGC1α, PPAR γ, AceCSI	FOXO3a induces cell arrest, regulates SIRT1 expression and cell proliferation	Bladder carcinoma and other types	
	Suppressor	Atg5, Atg7, and Atg8	↓ SIRT1 resulted in ↓ autophagy. SIRT1 interacts with Atg5, Atg7, and Atg8, to regulate autophagy	Breast cancer, prostate cancer, and some other types	
	Suppressor	Smad3 and Smad7	Smad6 and Smad7, are key modulators of TGF-β. ↑ SIRT1 led ↓ Smad7 levels TGF-β–induced mesangial cell apoptosis, whereas ↓ SIRT1 ↑ poptosis	Lung cancer	
	Suppressor	β-catenin, DKK1, and Dvls	SIRT1 ↓ dea cetylation of β-catenin and drives cell proliferation. ↓ SIRT1 ↑ DKK1 expression	Prostate cancer, breast cancer, ovary cancer, and melanoma	
	Suppressor	RelA/p65	SIRT1 regulates RelA/p65 NF-κB both in vitro and in vivo. (BCA3) has been reported to ↓ NF-κB–dependent transcription by binding to p65	Lung cancer, breast cancer and other types of cancer	
	Suppressor	Ku70, XPA, XPC, and NBS1	SIRT1 may act as a tumor suppressor. XPC is a substrate of SIRT1 and ↑ its expression	Hepatic carcinoma, skin cancer	
SIRT2 deacetylases	Supressor	CDH1/CDC20	SIRT2 ↓ causes ↑ levels of Aurora-A and spontaneous tumor formation. SIRT2 ↓ the viability of human breast cancer cells via ↓ c-Myc expression	Breast cancer	(Zhang et al. 2020b)
	Promoter	ALDH1A1	SIRT2 protein levels were significant ↑ in $ALDH1^+$ CSCs. NOTCH-induced SIRT2 deacetylation activity on K353 of ALDH1A1 led to enzymatic activation to sustain breast CSCs	Breast cancer	
	Promoter	Akt, PEPCK1	↓ SIRT2 impaired Akt/GSK-3β/β-catenin-signaling cascade and ↑ increased PEPCK1	Liver cancer	
	Promoter	JAJD2A	SIRT2 bound to JMJD2A express negatively, which led to the × of NSCLC cell proliferation, and tumor growth	Lung cancer	
	Suppressor	MEK1	SIRT2 × MEK1 activation and loss of SIRT2 led to ↑ MEK1 and ↓ tumor	Colon cancer	
	Suppressor	NFκB/CSN2	SIRT2-specific inhibitor inactivates the NFκB/CSN2 to ↑ G1 arrest which potently × tumor growth	Colon cancer	

Table 3 (continued)

Type of SIRT	Activity	Target	Regulation	Cancer	Ref
SIRT3 deacetylases	Suppressor	PGC-1α	↑ of PGC-1α & SIRT3 cause apoptosis and ↓ proliferation in MCF-7 cell lines	Breast cancer and some others	(Xin and Lu 2020)
	Suppressor	Notch-1	SIRT3 causes cell proliferation through ↓ Notch-1	Gastric cancer	(Wang et al. 2018e)
	Suppressor	Wnt/β-catenin ^{p}	SIRT3 ↓ Wnt/β-catenin ^{p} and by regulation FoxO3a	Prostate cancer	(Radini et al. 2018)
	Suppressor	HIF-1 α	SIRT3 acts as a tumor suppressor by ↓ ROS and activates HIF-1α	Renal carcinoma cells	(Jeh et al. 2017)
	Suppressor	Pfn1	Pfn1 regulates SIRT3 expression and this causes destabilization of HIF1α	Pancreatic cancer	(Yao et al. 2014)
	Promotor	ZEB1	ZEB1 regulates aerobic glycolysis by ↓ SIRT3	Pancreatic cancer	(Xu et al. 2018)
	Suppressor	GSK-3β/BAX ^{p}	SIRT3 cause intracellular acidification which activates BAX. Cause apoptosis	Hepatocellular carcinoma	(Yan et al. 2018)
	Promoter	NMNAT2	↓ of SIRT3 inhibit NMNAT2. and this ↓ of SIRT3 cause apoptosis	Non-small lung carcinoma cells	(Li et al. 2013)
	Suppressor	PI3K/AKT^{p}	↑ of SIRT3 × the PI3K/AKT pathway and × tumor growth	Pancreatic cancer cells Hepatocellular carcinoma	(Quan et al. 2015b)
	Suppressor	c-MYC	↑ of SIRT3 × c-MYC and PI3K/AKT pathway	Prostate cancer	(Quan et al. 2015a)
	Suppressor	GOT2	Deacetylation of GOT2 inactivates the malate-aspartate shuttle	Pancreatic cancer	(Yang et al. 2015b)
	(I)Promotor (ii)Suppressor	P53	SIRT3 and BAG 2 inactivate the p53	Bladder cancer	(Yang et al. 2015b)
	Suppressor	P21	SIRT3 ↑ p21 and ↓ ROS level. Thus, inducing apoptosis and × tumor growth	Lung adenocarcinoma, melanoma, breast cancer, and some others	(Xiao et al. 2013)
	Promotor	RIPK2	↑ inhibits RIPK2 mediated necroptosis	Prostate cancer	(Fu et al. 2020)
	Promotor	KU70	SIRT3 deacetylates ku70. × of ku70 cause cell growth and apoptosis	Glioma; cardiomyocytes	(Zhao et al. 2018) (Sundaresan et al. 2008)
	Suppressor	JNK	SIRT3 ↓ GSTP1 which activates JNK activity. Drug sensitivity	Hepatocellular carcinoma	(Tao et al. 2016)
	Suppressor	MPC1	SIRT3 binds MPC1 and ↑ its functions	Colon cancer	(Liang et al. 2015)

Table 3 (continued)

Type of SIRT	Activity	Target	Regulation	Cancer	Ref
SIRT4 deacetylases	Suppressor	E-cadherin	SIRT4 ↑ E-cadherin expression by ↓ glutamine metabolism	Colorectal cancer and others	(Miyo et al. 2015)
	Suppressor	Il6-stat3 ^{p}	↑ tamoxifen sensitivity to breast cancer by × il6-stat3 pathway	Breast Cancer	(Xing et al. 2019a)
	Suppressor	Fis1	× Drp1, also ↓ MEK/ERK activity	NSCLC	(Fu et al. 2017a)
	Indirectly promotor	SET8/KLF4	SET8 inactivates KLF4 and this inactivates SIRT4	Hepatocellular cancer	(Chen et al. 2019a)
	Indirectly promotor	UHRF1	UHRF1 promotes aerobic glycolysis and this × SIRT4 and causes cell growth	Pancreatic cancer cells	(Hu et al. 2019a)
	Suppressor	GDH	SIRT4 × proliferation and induce apoptosis by inhibiting glutamine metabolism	Thyroid cancer tissue	(Chen et al. 2019c)
	Indirectly promotor	CtBP	CtBP ↑ GDH activity and this ↓ SIRT4	Different cancers	(Wang et al. 2018a)
	Suppressor	ANT2	SIRT4 ↓ the acetylation of ANT2. PAK6 phosphorylates ANT2. Cause apoptosis	Prostate cancer	(Guan et al. 2020)
SIRT5 deacetylases	Promotor	NRF2	It regulates the expression of genes involved in cellular homeostasis	NSCLC cells	(Lu et al. 2014)
	Promotor	CDK1	CDK1 × SIRT5 and ↑ aerobic glycolysis	Gastric cancer	(Tang et al. 2018)
	Suppressor	OGDH	SIRT5 desuccinylates OGDH and inactivates it, × mitochondrial functions	Gastric cancer	(Lu et al. 2019)
	Promotor	ACOX1	↓ of SIRT5 ↑ activation of ACOX1 and this ↑ H2O2. Cellular progression	Hepatocellular cancer	(Chen et al. 2018)
	Promotor	LH	SIRT5 deacetylates LBDH and ↑ tumorigenesis	Colorectal cancer	(Shi et al. 2019)
	Promotor	E2F1	SIRT5 ↑ activates E2F1 causing HCC growth	Hepatocellular cancer	(Chang et al. 2018)
	Promotor	SUN2	SIRT5 ↑ downregulates SUN2	Lung cancer	(Lv et al. 2015)
	Promotor	SOD1	De-succinylation of SOD1 eliminates ROS	Lung cancer	(Lin et al. 2013)
	Promotor	SDHA	Desuccinylation of SDHA ↑ tumorigenesis	Renal cancer	(Ma et al. 2019)
	Promotor	GLS	Desuccinlation of GLS supports glutamine metabolism	Breast cancer	(Greene et al. 2019)
	Promotor	ACAT1	↑ of SIRT5 regulates ACAT1 and MAPK activity to promote proliferation	Prostate cancer	(Guan et al. 2020)
	Promotor	PMK2	SIRT5 desuccinylates PMK2 and inactivates it. ↑ ROS level	Colorectal cancer	(Xiangyun et al. 2017)

Table 3 (continued)

Type of SIRT	Activity	Target	Regulation	Cancer	Ref
SIRT6 deacetylases	Suppressor	HIF-1	↓ of myc-regulated genes, Warburg effect and tumor growth	Colorectal cancer	(Desantis et al. 2018)
	Suppressor	c-Jun-survivin	↑ c-Jun-survivin and by SIRT6 by c-fos-SIRT6	Liver cancer	
	Suppressor	USP10	↓ of deubiquitinase protein, USP10 antagonizes the transcriptional activity of c-myc-oncogene	Colon cancer	
	Suppressor	pAkt, HK2, PDHK1	↓ of RUNX2-mediated metabolic changes ↑ glycolytic protein level	Breast	
	Suppressor	E2F1	E2F1 binds with the SIRT6 promoter and ↓ its activity	Bladder and prostate cancer	
	Suppressor	NOTCH3	↓ of expression by inhibition of proliferation	Ovarian cancer	
	Suppressor	PKM2	Inhibition of cell proliferation and tumorigenesis via nuclear pyruvate kinase M2	Hepatocellular carcinoma	
	Promoter	CD34 +	In CD34 + blasts, SIRT6 affects DNA damage and intense replicative stress	Acute myeloid leukemia	
	Promoter	p53 and E2F1	Deacetylation of H3K9 blocking transcription and enhancing chromatin accessibility	Hepatocellular carcinoma	
SIRT7 deacetylases	Suppressor	NCTD-PTX	NCTD-PTX Combination and regulation significantly ↑ cell arrest	Prostate cancer	(Blank and Grummt 2017)
		p53, PCAF	SIRT7 directly interacts with p300/CBP-associated factor causing ↑ expression of p21Waf1/Cip1 causing cell arrest	MDM2 degradation	(Lu et al. 2020)

expression of tumor suppressor proteins like p53 and p16 (Xia et al. 2017). This overexpression results in the inhibition of cell growth during the G2/M phase and the induction of apoptosis in hepatocellular carcinoma (Huang et al. 2021). Intriguingly, a low level of SIRT5 heightens ACOX1 activation through succinylation, leading to increased H_2O_2 levels and the advancement of cellular progression in cancer cells (Chen et al. 2018). However, a contrasting recent report indicates exceptional upregulation of SIRT5 in HCC. Overexpressed SIRT5 activates E2F1, a pivotal player in cell cycle and proliferation. Conversely, SIRT5's inactivation of E2F1 yields adverse effects, ultimately promoting apoptosis (Chang et al. 2018). SIRT5 knockdown suppresses HCC cell proliferation, whereas SIRT5 overexpression promotes it (Zhang et al. 2019). SIRT5 downregulation also restrains HepG2 and MHCC97H cancer cell lines. The SNHG14 and lncRNA regulate the miR-656-3p/SIRT5 pathway, effectively impeding cell invasion and migration via ceRNA (Tang and Yang 2020).

Pancreatic cancer

SIRT3 experiences downregulation in pancreatic cancer cells, with a further decrease observed in advanced-stage cancer (Huang et al. 2017). A reduced level of SIRT3 promotes the acetylation of GOT2, while SIRT3 overexpression deacetylates and inactivates GOT2, leading to the inhibition of the malate aspartate shuttle. Consequently, overexpressed SIRT3 halts proliferation in pancreatic cancer cells (Yang et al. 2015b). Profilin-1 counters tumorigenesis by regulating SIRT3 levels, thereby destabilizing HIF-1α and effectively suppressing cancer and tumorigenesis (Yao et al. 2014). The suppression of SIRT3, orchestrated through zinc finger E box protein-1 and methyl-CpG binding protein 1, results in the upregulation of aerobic glycolysis (Xu et al. 2018). Ubiquitin ring-like finger protein 1 propels aerobic glycolysis, which in turn inhibits SIRT4 and fosters enhanced cell proliferation in pancreatic cancer cells. The inhibition of aerobic glycolysis and the suppression of cell proliferation can be achieved by silencing UHRF1 (Hu et al. 2019a). Branched-chain amino acid transaminase-2 (BCAT2) catalyzes the catabolism of branched-chain amino acids (BCAAs). SIRT4 acts on BCAT2 by deacetylating it and stabilizing it at K44. The acetyltransferase for BCAT2 is a cAMP-responsive element-binding protein-binding protein. Deprivation of branched-chain amino acids prompts BCAT2 acetylation, leading to its subsequent degradation via the ubiquitin–proteasome pathway (Lei et al. 2020).

Lung cancer

The level of SIRT3 is found to be downregulated in human lung adenocarcinoma. However, its overexpression enhances the bax/bcl and bad/bcl -x/l ratios. This overexpression also upregulates the tumor suppressor proteins p53 and p21, leading to decreased cellular ROS levels and the suppression of tumor proliferation in lung adenocarcinoma (Xiao et al. 2013). Conversely, SIRT3 is highly expressed in non-small cell lung adenocarcinoma (Gong et al. 2018). In NSCLC, SIRT3's overexpression inhibits NMNAT2 and NAD^+ acetylation, effectively inhibiting the growth and proliferation of NSCLC cells (Li et al. 2013). SIRT3 presents a dual role in lung cancer, acting both as a promoter and a suppressor. A low level of SIRT4 leads to lung tumor progression in mice. Its diminished expression also enhances glutamine-dependent proliferation. Therefore, the upregulation of SIRT4 inhibits proliferation and tumor growth in lung cancer (Jeong et al. 2013b). Overexpression of SIRT4 inhibits Drp1 phosphorylation through its interaction with Fis1. Additionally, SIRT4 regulates MEK/ERK activity, ultimately suppressing cell proliferation (Fu et al. 2017b). SIRT5 is found to be overexpressed in lung cancer, and its downregulation suppresses cell growth (Lv et al. 2015). SAD1/UNC84 domain protein 2 inhibits cancer cell proliferation in lung cancer and enhances sensitivity to chemotherapy drugs. However, overexpression of SIRT5 leads to the downregulation of SUN2 (Lv et al. 2015). In cases where SIRT5 is knocked off, lung cancer cells show heightened responsiveness to medication therapy. SIRT5 mRNA levels are also linked to NRF2 expression, and SIRT5 knockdown leads to lower NRF2 expression and its downstream drug resistance genes (Lu et al. 2019). Succinylation of SOD1 suppresses the growth of cancer cells, but SIRT5 de-succinylates and activates SOD1, eliminating ROS and acting as a tumor promoter (Lin et al. 2013). SIRT5 downregulation has been observed in the lung cancer cell line A549, preventing it from deacetylating signal transducer and activator of transcription 3 and leading to its activation (Xu et al. 2016).

Gastric cancer

The global prevalence of gastric cancer (GC) is experiencing a decline; however, the quality of life and survival duration for certain GC patients remains poor. Elevated expression of SIRT1 has been associated with cell invasion, epithelial-mesenchymal transition, and poor prognosis (Hu et al. 2020). SIRT3's downregulation in gastric cancer is linked to the Krebs cycle, oxidative phosphorylation, and acid metabolism (Fernández-Coto et al. 2018). Overexpression of SIRT3 inhibits cell proliferation and induces apoptosis by downregulating Notch-1 (Hu et al. 2018). SIRT3 overexpression enhances cancer cell growth by increasing ATP synthesis through glycolysis, glucose absorption, MnSOD activity, and lactate formation. Conversely, SIRT3 knockdown diminishes all of these parameters (Cui et al. 2015). Overexpression of mammalian sterile 20-like kinase

1 controls mitochondrial fission by suppressing the AMPK/SIRT3 pathway. Activation of the AMPK-SIRT3 pathway counteracts Mst1 overexpression-induced mitochondrial fission. Downregulation of SIRT3 in gastric cancer cells results in increased HIF-1α expression, while its upregulation suppresses cell proliferation (Yang et al. 2014b).

SIRT4 experiences downregulation in gastric cancer cells (Liang et al. 2015). In gastric adenocarcinoma cells, SIRT4 suppresses cell proliferation by regulating the cell cycle. Overexpression of SIRT4 curbs cell growth by inhibiting extracellular signal-regulated kinase, cyclin D, and cyclin E, thus impairing the colony-forming ability of gastric cancer cells (Hu et al. 2019b). Low SIRT4 expression correlates with tumor size, pathology grade, and lymph node involvement, all indicative of a poor prognosis (Sun et al. 2018). The cell cycle-dependent kinase CDK1 suppresses SIRT5, consequently upregulating aerobic glycolysis and promoting cell proliferation in gastric cancer. Inhibition of CDK1 leads to SIRT5 upregulation, halting aerobic glycolysis and suppressing cell proliferation (Tang et al. 2018). Desuccinylation of 2-oxoglutarate dehydrogenase inactivates it and thus suppresses cell proliferation in gastric cancer cells (Lu et al. 2019). SIRT5 promotes autophagy through activated protein kinase AMPK, and SIRT5 is degraded during apoptosis in gastric cancer cell lines (Gu et al. 2021).

Colorectal cancer

Colorectal cancer ranks as the third most common cancer worldwide (Sung et al. 2021). SIRT3 exhibits high expression, while SIRT4 is downregulated in colorectal cancer cells (Huang et al. 2016). The suppression of SIRT3 leads to inhibited cell proliferation, growth, development, and migration of colorectal cancer cells (Liu et al. 2014). Acetylation of serine methoxy methyltransferase-2 activates it and restrains cell proliferation while reducing NADH levels. Elevated SIRT3 levels counteract acetylation in colorectal cancer (Wei et al. 2018). Acetylation of MPC1 inactivates its function in controlling cancer cell growth in colon cancer. SIRT3 binding to MPC1 leads to its deacetylation and enhancement of function (Liang et al. 2015). The mitochondrial methylenetetrahydrofolate dehydrogenase (MTHFD2) regulates redox homeostasis and cell proliferation in colorectal cancer. Cisplatin inhibition of SIRT3 leads to the acetylation of MTHFD2 (Wan et al. 2020). SIRT3's impact on chemoresistance in colorectal cancer cells is mediated through the regulation of SOD2 and PGC-1α (Paku et al. 2021). Downregulation of SIRT3 activates mitochondrial fission by suppressing the Akt/PTEN pathway. Elevated SIRT3 levels and reactivation of the Akt/PTEN pathway enhance colorectal cancer cell mobility and survival (Wang et al. 2018e). SIRT3's deacetylation of different proteins, such as NEIL1, NEIL2, OGG1, MYTYH, APE1, and LIG3, contributes to the regulation of DNA repair activity in colorectal cancer (Kabziński et al. 2019). SIRT4 upregulates E-cadherin expression, suppresses cell growth and proliferation in colorectal cancer by inhibiting glutamine metabolism, and regulates the AKT/GSK3β/cyclin D pathway (Wang et al. 2018f).

SIRT5 is upregulated in colorectal cancer. SIRT5's deacetylation of LDHB enhances autophagy and promotes tumorigenesis in colorectal cancer (Shi et al. 2019). Overexpression of SIRT5 imparts resistance to chemotherapeutic drugs in colorectal cancer. De-malonylation of succinate dehydrogenase-A inactivates it, leading to succinate accumulation (Du et al. 2018). SIRT5 de-glutarylates glutamate dehydrogenase 1, activating it and promoting carcinogenesis in colorectal cancer (Wang et al. 2018f). SIRT5's de-succinylation of serine hydroxymethyltransferase-2 (SHMT2) increases its activity in colorectal cancer cell lines (Yang et al. 2018a). SIRT5 de-succinylates pyruvate kinase M2, inhibits its activity, elevates reactive oxygen species levels, and enhances cell proliferation and growth in colorectal cancer cells. SIRT5 silencing inhibits cell proliferation and invasion (Xiangyun et al. 2017).

Prostate cancer

Prostate cancer stands as one of the most frequently occurring cancers in men and is among the leading causes of cancer-related deaths worldwide (Siegel and Miller 2020). In prostate cancer, SIRT3 is downregulated, and its expression becomes comparatively high during the metastatic phase. Overexpression of SIRT3 inhibits the Wnt/β-catenin pathway and, through the regulation of FoxO3a, suppresses cancer cell migration in prostate cancer (Radini et al. 2018). A high expression level of SIRT3 inhibits Akt phosphorylation, leading to the inhibition of the c-MYC oncoprotein. The growth and proliferation of prostate cancer cells are hindered by the inhibition of the PI3K/Akt pathway (Quan et al. 2015a). Histone deacetylase-2 is activated by the binding of steroid receptor coactivator-2 and the androgen receptor (AR), which inhibits SIRT3 and activates acetylated mitochondrial aconitase-2, thereby facilitating or enhancing the proliferation of prostate cancer cells (Sawant Dessai and Dominguez 2021). In contrast, Weiwei and colleagues reported that SIRT3 and SIRT6 act as tumor promoters, contributing to tumor progression by inhibiting RIPK2-necroptosis. Downregulation of both SIRTs activates TNF-induced necroptosis (Fu et al. 2020). While SIRT3 is upregulated in prostate cancer, inhibiting it using an inhibitor leads to decreased cell growth and progression in prostate cancer cells (Singh et al. 2018). SIRT4 serves as a suppressor in prostate cancer. Overexpression of SIRT4 inhibits ANT2, thereby suppressing cell proliferation and growth. ANT2 positively correlates with PAK6, and SIRT4 suppresses the

acetylation of ANT2. PAK6 phosphorylates ANT2, inducing apoptosis (Guan et al. 2020). SIRT5 is upregulated in prostate cancer cells. It regulates the activity of acetyl-CoA acetyltransferase 1 and the mitogen-activated protein kinase pathway, thereby enhancing the ability of cancer cells to grow and proliferate (Guan et al. 2020).

Renal cell carcinoma

SIRT3 expression is downregulated in renal cell carcinoma. Overexpression of SIRT3 leads to an increase in mitochondrial mass and cellular ROS levels in renal cancer cells, reversing the Warburg effect. It also promotes mitochondrial biogenesis through the deacetylation of TFAM (Liu et al. 2018a). However, it is worth noting that SIRT3 is also found to be upregulated in renal cell carcinomas (RCCs), where it enhances cancer cell proliferation by increasing the activity of glutamate dehydrogenase. Depletion of SIRT3 suppresses glutamate dehydrogenase activity and inhibits cell proliferation (Choi et al. 2016). SIRT3 can act as a tumor suppressor by suppressing ROS and activating HIF-1α in renal cell carcinoma (Jeh et al. 2017). SIRT4 is downregulated in renal cell carcinoma, exhibiting significantly lower expression compared to normal tissues. Knockout of SIRT4 enhances cancer cell proliferation, migration, and invasion, while upregulation of SIRT4 inhibits cell proliferation in renal cell carcinoma (Xuan et al. 2020). Overexpression of SIRT4 upregulates HO-1 in von Hippel-Lindau proficient cells and inhibits its expression in VHL deficient cells. SIRT4 plays a role in regulating ROS and HO-1 production by facilitating the phosphorylation of p38-MAPK (Tong and Kai 2021). SIRT5 is upregulated in renal carcinoma cells. It de-succinylates SDHA, thereby enhancing tumorigenesis in renal carcinoma cells (Ma et al. 2019). In the context of treatment, a tyrosine kinase inhibitor called sunitinib is used as a first-line treatment against clear cell renal cell carcinoma. Disruption in the regulation of the SIRT5/IDH2 pathway is associated with sunitinib resistance in renal cancer cells (Meng and Chen 2021).

Ovarian cancer

It is a female-specific cancer. In ovarian cancer, SIRT3 expression is downregulated, while SIRT5 expression is upregulated (Zhang et al. 2020c). Overexpression of SIRT3 in patients is associated with better survival outcomes (Chen et al. 2019c). SIRT3 is also downregulated in metastatic tissues and metastatic cell lines of ovarian cancer. Its reduced expression level promotes migration and invasion of cancer cells. Overexpression of SIRT3 suppresses the epithelial-to-mesenchymal transition by inhibiting twist in ovarian cancer cells (Dong et al. 2016). Treatment with cisplatin, in combination with ABT737, enhances apoptosis and reduces mitochondrial membrane potential. SIRT3 expression also increases the sensitivity of ovarian cancer cells to cisplatin treatment (Wang et al. 2019a). SIRT3 overexpression and SIRT3-mediated oxidant scavenging are crucial for anoikis resistance after matrix detachment, and both SIRT3 and SOD2 are necessary for colonization of ovarian cancer cells (Kim et al. 2020). Cryptotanshinone is a therapeutic agent used in various cancers. In ovarian cancer cells, CT suppresses glucose uptake and lactate production. It exerts its antitumor activity by targeting the STAT3/SIRT3/HIF-1α pathway and inhibiting glycolysis, growth, and proliferation of ovarian cancer cell lines (Yang et al. 2018b). PKMYT1 enhances the progression and proliferation of ovarian cancer cells by targeting SIRT3 (Xuan et al. 2020). SIRT5 overexpression confers resistance to chemotherapeutic drugs like cisplatin by reducing DNA damage in a ROS-dependent manner through the NRF2/HO-1 pathway, which subsequently upregulates glutathione, a ROS scavenger (Sun et al. 2019b).

Thyroid cancer

SIRT3 and nicotinamide phosphoribosyltransferase are upregulated, while SIRT4 is downregulated in thyroid cancer (Shackelford et al. 2013). Overexpression of microRNA miR-1225-5P inactivates the Wnt/β-catenin pathway by directly targeting SIRT3, leading to the inhibition of tumor cell proliferation, invasion, and migration (Wang et al. 2019b). Both SIRT1 and SIRT3 may contribute to the resistance to apoptosis induced by genotoxic drugs (Kweon et al. 2014). Overexpression of SIRT4 inhibits cancer cell proliferation, invasion, and migration by suppressing glutamine metabolism. Additionally, it suppresses the G0/G1 phase of the cell cycle (Chen et al. 2019c). GDH also stimulates glutaminolysis, which provides an alternative energy source for cancer cells, as glutamine is metabolized to aspartate, forming oxaloacetate, malate, and ultimately pyruvate. This process promotes the NADP/NADPH ratio and maintains redox equilibrium. The field of SIRT5 research remains open for further investigation.

Leukemia

SIRT3 and SIRT4 are downregulated in B cell malignancy, while SIRT5 is upregulated in myeloid leukemia. Loss of SIRT3 enhances proliferation and growth through a ROS-dependent mechanism. Upregulation of SIRT3 acts as a tumor suppressor in B cell malignancy leukemia and relies on the deacetylation of IDH2 and SOD2 (Yu et al. 2016). Albendazole primarily induces the death of U937 cells through the SIRT3/ROS/P38 MAPK/TTP axis-mediated TNF upregulation, and the downregulation of SIRT3 caused by albendazole enhances its microtubule-destabilizing effect

(Wang et al. 2019a). Autophagy maintains the ubiquitination-proteasomal degradation of SIRT3 to control lipid oxidative stress. This indicates a process in which autophagy collaborates with the ubiquitination-proteasomal system to regulate oxidative stress by controlling the levels of certain proteins in K562 leukemia cells (Fang et al. 2016). Overexpression of SIRT4 inhibits cell proliferation, growth, and migration (Bradbury et al. 2005). SIRT4 suppresses Myc-induced B cell lymphomagenesis by inhibiting glutamine metabolism (Jeong et al. 2014). SIRT5 downregulation suppresses proliferation, inhibits colony formation, and induces apoptosis in 18 out of 25 cell lines.

Esophageal cancer

SIRT3 is highly upregulated, while SIRT4 is downregulated in esophageal cancer. Therefore, patients with a high level of SIRT3 and a low level of SIRT4 have a lower chance of survival (Zhao et al. 2013), whereas SIRT4's downregulation inhibits cell proliferation (Yang et al. 2014a). SiRNA-mediated downregulation of SIRT3 expression enhances apoptosis in esophageal cancer cells. The decrease in SIRT3 levels leads to an increase in the expression of p21 and Bax but decreases the level of the Bcl2 protein (Yang et al. 2014a). Knockdown of SIRT4 enhances glutamate dehydrogenase activity and promotes cell survival, proliferation, and migration (Nakahara et al. 2016). In contrast to this study, Lai and colleagues argued that SIRT4 is highly expressed in Chinese patients with esophageal cancer (Lang and Piekorz 2017). As of now, there is no research work related to SIRT5 and esophageal cancer.

Skin cancer and types

Skin cancer is the most common type of human cancer and is divided into three main types: (i) melanoma, (ii) cutaneous squamous cell carcinoma, and (iii) basal cell carcinoma (BCC). Altered cellular metabolism and epigenetic abnormalities may provide the rationale for the role of SIRTs in skin carcinomas, in addition to UV-induced DNA mutations (Pfeifer and Besaratinia 2012). Clinically, a strong link between elevated levels of skin squamous cell carcinoma and SIRT6 has been identified (Sun et al. 2019a). SIRT6 enhances cell proliferation by acting as an oncogene, upregulating COX-2, and thus suppressing AMPK signaling. Furthermore, the expression of SIRT6 in skin keratinocytes could be enhanced by the activation of the AKT pathway due to exposure to UVB light (Zhang and Qin 2014). We have discussed the role of SIRTs in all three types of skin cancers.

Melanoma

SIRT3 is upregulated in various melanoma cells at both RNA and protein levels. Overexpression of SIRT3 enhances proliferation in Hs294T cells and Mel-ST melanocytes. Conversely, its low expression inhibits proliferation in melanoma cells (George et al. 2016). SIRT3 and MnSOD work together to regulate ROS levels, thereby enhancing cell proliferation and development in melanoma cells (Torrens-Mas et al. 2020). SIRT3 upregulates p21 and decreases ROS levels, inducing apoptosis and inhibiting tumor growth in melanoma cells (Xiao et al. 2013). The functions of SIRT4 in relation to melanoma have not been extensively explored, but a study showed that SIRT4 is upregulated in melanoma cancer cells following treatment with the chemotherapeutic drug melphalan (Wouters et al. 2012). Another study demonstrated that downregulation of SIRT5 inhibits proliferation in melanoma cells, and it promotes melanoma cell survival by regulating glucose and glutamine metabolism (Park et al. 2016). However, a separate study revealed that SIRT5 depletion does not significantly affect cancer cell progression or proliferation in melanoma cells with the $BRAF^{V600E}$ mutation (Moon et al. 2019).

Basal cell carcinoma

BCC originates from keratinocytes located in the basal layer of the epidermis. This type of cancer affects millions of people worldwide (Rogers et al. 2015). SIRT3 mRNA is found to be downregulated in basal cell carcinoma, and its potential upregulation might induce apoptosis or inhibit cell proliferation in BCC (Temel et al. 2016). Currently, there is no available literature pertaining to SIRT4, SIRT5, and their relationship with basal cell carcinoma. This area of research remains open for exploration and investigation.

Head and neck cancer

Mitochondrial SIRTs are found to be downregulated in head and neck cancer (Lai et al. 2013). The decreased expression of SIRT3, SIRT4, and MTUS-1 genes has been linked to a reduction in the expression of the DNA repair gene OGG1-2a, while concurrently increasing the proliferation of squamous cell carcinoma of the head and neck (Mahjabeen and Kayani 2016). Research indicates that inhibitors of SIRT 3, such as LC-0296, effectively suppress cell growth, survival, and proliferation, thereby promoting apoptosis in HNSCC (Alhazzazi et al. 2016). Moreover, heightened expression of oxidative phosphorylation contributes to cell survival and proliferation in squamous cancer cells of the head and neck (Frederick and Skinner 2020).

Endometrial cell

SIRTs play a pivotal role in processes such as metabolism, aging, and hormonal balance, all of which are critical for the development of endometrial cancer. While SIRT1 might

potentially accelerate the growth of endometrial tumors, other SIRTs may contribute to endometriosis and the endometrial receptivity of embryos. SIRT3's significance seems limited, whereas SIRT4 and SIRT5 are downregulated in endometrial cell carcinoma (Bartosch et al. 2016). PGC-1α and SIRT3 are notably upregulated in endometrial carcinoma cells, contributing to the elevated malignancy in EC. The collaborative impact of PGC-1α and SIRT3 plays a crucial role in the progression and growth of EC (Dai et al. 2017). Notably, the overexpression of SIRT7 has been observed in EC, and its downregulation diminishes invasiveness and growth in EC by decreasing NF-κB expression. In essence, SIRT7 might emerge as a potential therapeutic target for EC treatment (Fan et al. 2018).

Cervical cancer

SIRT3 is upregulated and regulates fatty acid synthesis in cervical cancer cells by increasing the expression level of ACC1, thereby enhancing SIRT3 deacetylation-induced lipogenesis. This critical role in proliferation is evident in cervical cancer cells (Xu et al. 2020). The PI3K E542K and E545K/β-catenin/SIRT3 signaling pathway controls glucose metabolism and plays a significant role in regulating proliferation and development in cervical cancer. β-catenin suppresses SIRT3 activity, leading to decreased glucose uptake (Jiang et al. 2018). The combination of the drugs metformin and nelfinavir increases the expression of SIRT3 and MICA, rendering human cervical cancer cells sensitive to NK cell lysis. This drug combination enhances SIRT3/mROS-mediated autophagy in cervical cancer (Xia et al. 2019). Vosaroxin, a chemotherapeutic drug, targets the SIRT3/Hif1-α pathway and induces cytotoxic effects in cervical cancer (Zhao and Yu 2018). Programmed death-ligand-1 (PD-L1) promotes the growth and development of cervical cancer by regulating the ITGB4/SNAI1/SIRT3 pathway. The upregulation of PD-L1 increases glucose uptake and enhances metastasis (Wang et al. 2018c). The upregulation of SIRT3 enhances the activation of the AMPK/PPAR pathway, which is involved in lipid metabolism and promotes metastasis in cervical cancer cells (Xiao et al. 2020). As for SIRT4 and SIRT5, their investigation about cervical cancer remains pending.

Bladder cancer

Bladder cancer ranks as the ninth most common type of cancer, resulting in 160,000 deaths and an estimated 400,000 new cases annually worldwide across both genders (Monteiro-Reis and Lameirinhas 2020). SIRT1 is linked to bladder cancer tumorigenesis and demonstrates a positive association with chemo-resistance and inadequate diagnosis (Hu et al. 2014). SIRT3 partially suppresses the activity of p53, contributing to the growth and development of bladder cancer cells. Both SIRT3 and BAG-2 contribute to p53 inactivation. The deacetylation of p53 facilitates the growth and proliferation of bladder cancer cells (Li et al. 2010). SIRT4 experiences downregulation in bladder cancer (Blaveri et al. 2005). UNC5B and SIRT4 serve as downstream targets of miR-424. Cisplatin suppression in bladder tumor tissues is hindered by miR-424. The downregulation of SIRT4 results in decreased cisplatin-induced proteolytic cleavage of PRAP, reducing the sensitivity of these cells to cisplatin (Yu et al. 2020). In the context of bladder cancer, the expression of SIRT1, SIRT2, SIRT4, and SIRT5 was significantly lower, while SIRT6 and SIRT7 were higher in BIC (Monteiro-Reis and Lameirinhas 2020).

Neuroblastoma

Neuroblastoma originates from the adrenal glands but can manifest in various locations like the chest, abdomen, or neck. SIRT3 experiences upregulation in neuroblastoma, and its downregulation results in increased apoptosis. Reduced SIRT3 expression leads to elevated ROS levels, while diminishing SOD1 and GSH levels ultimately leading to mitochondrial membrane potential collapse (Zhang et al. 2018). The upregulation of SIRT3 promotes LKB1 phosphorylation, which activates AMPK, subsequently suppressing mTOR phosphorylation. This pathway induces autophagy in SH-SY5Y cells. Conversely, SIRT3 downregulation diminishes the effectiveness of rotenone and results in cell apoptosis (Zhang et al. 2018). In motor neuronal cells (NSC34) under oxidative stress, both SIRT3 and CARM1 expressions decrease. Pretreatment of these neuroblastoma cell lines with lithium triggers cytotoxicity and elevates the levels of SIRT3 and CARM1 (Wang et al. 2013). SIRT4 is downregulated in neuroblastoma cells, with lower expression observed in patients with lymph node metastasis compared to those without. Elevated SIRT4 levels inhibit cell proliferation, invasion, metastasis, and also reduce energy generation in neuroblastoma cells (Wang et al. 2018d). SIRT5 exhibits upregulation in cultured SH-EP neuroblastoma cells, and reducing ROS levels safeguards these cells from apoptosis (Liang et al. 2015).

Glioma

SIRT3 experiences downregulation in glioma brain cancer cells; hence, patients exhibiting high levels of SIRT3 tend to have shorter survival times. SIRT3 plays a role in deacetylating Ku-70, stabilizing the interaction between Ku-70 and BAX, consequently reducing cell apoptosis (Luo et al. 2018). Linalool diminishes cell viability in U87-MG cells and heightens the expression of bax/bcl-2, while decreasing the expression of bcl-2/bcl-xl, thereby promoting apoptosis.

Linalool also downregulates the interaction between SIRT3 and SOD2. Overexpressing SIRT3 counteracts the inhibition caused by linalool (Choi et al. 2016). The interaction between mitochondrial chaperone TRAP1 and mitochondrial SIRT 3 augments mitochondrial respiration and diminishes the level of reactive oxygen species (ROS). Disruption of TRAP1 and SIRT3 leads to mitochondrial dysfunction, suppressing tumor formation in glioma cells (Park et al. 2019). Exendin-4 hampers migration and invasion through the GLP-1R/SIRT3 pathway in glioma cells (Nie et al. 2018). SIRT3 phosphorylates p53 and lowers the expression of MYR-NLs. MYR-NLs curtail glioma cell growth by controlling p53/SIRT3-induced PI3-K/AKT ERK pathways (Wang et al. 2018d). SIRT4 prevents glutamine formation and excitotoxicity through the regulation of glutamate metabolism and GDH activity (Yalçın and Colak 2020). Overexpressing SIRT4 inhibits GDH activity, consequently suppressing cell proliferation and growth in glioma cells (Zhang et al. 2016). SIRT5 is elevated in glioblastoma cancer cells, and its expression level is inversely linked to DNA methylation. Its upregulation results in the inhibition of cell proliferation in glioma cells (Chen et al. 2019b).

Tongue and oral cancer melanoma

SIRT3 experiences upregulation in oral cancer cells. SIRT3 is responsible for regulating Fis-1 expression through the c-jun N-terminal kinase (JNK) pathway. Notably, the downregulation of SIRT3 via the Fis-1/JNK pathway significantly contributes to the suppression of tongue cancer cells (Zhu et al. 2017). In the context of tongue and oral cancer, SIRT3 serves as a tumor promoter, inducing carcinogenesis and fostering cell proliferation. On the flip side, the downregulation of SIRT3 curbs oral cancer cell proliferation (Alhazzazi et al. 2011). SIRT3 exerts its influence by reducing the catalytic activity of specific proteins, thereby affecting redox metabolism. This inhibition of SIRT3 results in the attenuation of cell growth and proliferation while concurrently decreasing the levels of reactive oxygen species (ROS) in oral cancer cells (Chen et al. 2013). As of now, there is no available literature connecting SIRT4 and SIRT5 with tongue and oral cancer.

Cardiomyocytes

SIRT3 safeguards cardiomyocytes against oxidative stress and apoptosis through the modulation of the NF-κB pathway (Chen et al. 2013). Through its deacetylation of KU-70, SIRT3 enhances the interaction between KU-70 and Bax protein, resulting in an elevated expression of SIRT3 that safeguards cardiomyocytes from oxidative stress conditions (Sundaresan et al. 2008). In the realm of hypoxia-induced cardiomyocyte apoptosis, SIRT4 emerges as a pivotal player. It exerts influence on H9c2 cell viability and the activity of caspase 3/7. Furthermore, SIRT4's effects extend to the modulation of pro-caspase 9/caspase 9, pro-caspase 3/caspase 3, and Bax translocation (Liu et al. 2013). Downregulation of SIRT5 causes reduced cell viability and increases the number of apoptotic cells. SIRT5 regulates oxidative stress and induces apoptosis in cardiomyocytes (Liu et al. 2013). The involvement of SIRT(1–7) leads to different outcomes—promotion or suppression—in various cancers, which are concisely summarized in Fig. 3.

Therapeutic targets of SIRTs

Due to their dual nature, SIRTs have garnered significant attention as potential targets for drug development. A wide array of inhibitors and activators has been identified (Table 4) which laid down the foundation for studying the functions of SITRs and potentially as a treatment for different diseases in different conditions. Currently, repositioning study was performed to investigate the pan inhibitors of SIRT (Sarı et al. 2021). Particularly, 1502 sets of FDA-approved drugs were screened using three different software as AutoDock Vina/PyPx (Dallakyan and Olson 2015), Glide (Friesner et al. 2004), and FRED (McGann 2012) against the crystal structure of SIRTs, and the consensus score was generated by taking the average of these three score values. Based on these consensus scores, the top pan-SIRT inhibitors were indacaterol, alosetron, and cinacalcet. The therapeutic potential of these selected inhibitors was confirmed by in vitro studies.

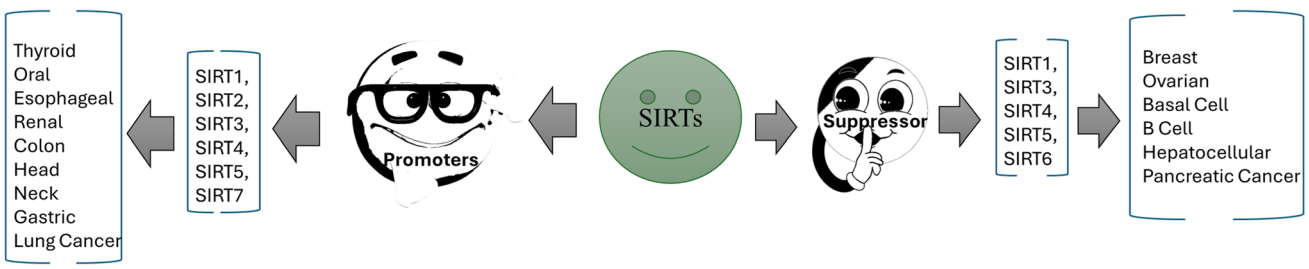


Fig. 3 Schematic representation of sirtuins-related different cancers based on their upregulation and downregulation

Table 4 Therapeutic potentials of different types of inhibitors and activators of sirtuins

Types	Compound	Activity	SIRTs	Ref
Resveratrol-related therapeutics	Stilbene resveratrol	Inhibition	SIRT3	(Gertz et al. 2012)
		Activation	SIRT5	
	Piceatannol	Activation	SIRT1,3,5	
	4′-bromo resveratrol	Inhibition	SIRT1,3	(George et al. 2019)
	SDX-437	Inhibition	SIRT3	(Patel et al. 2022)
	1,4-dihydropyridine (DHP)	Activation	SIRT3	(Mai et al. 2009)
	Honokiol	Activation	SIRT3	(Pillai et al. 2017)
Peptide inhibitors	Suramin	Inhibition	SIRT5	(Loharch et al. 2021)
	Thio-succinylated compounds	Inhibition	SIRT5	(Yang et al. 2017)
	Z-glutaryl CPS1 and 3-methyle 3-phenyl succinyl CPS1	Inhibition	SIRT5	(Roessler et al. 2014)
	SRT1720	Inhibition	SIRT3	(Gertz et al. 2013)
Nicotinamide inhibitors	EX-527	Inhibition	SIRT1,3	(Gertz et al. 2013)
	GW-5074	Inhibition	SIRT5	(Wang et al. 2022)
	ELT-11c	Inhibition	SIRT3	(Gertz et al. 2013)
	AGK2	Inhibition	SIRT2	(Outeiro et al. 2007)
	1,4-dihydropyridine	Inhibition	SIRT1/SIRT2	(Mai et al. 2009)
	AK7	Inhibition	SIRT2	(Taylor et al. 2011)
	2-anilinobezamide	Inhibition	SIRT1	(Suzuki et al. 2006)
Protein promoter	CyclinB1	Inhibition	SIRT4	(Huang et al. 2021)
Aurora kinase inhibitor	Alisertib	Inhibition	SIRT1	(Wang et al. 2015)
Deacetylase inhibitor	Sirtinol	Inhibition	SIRT1	(Kang et al. 2022)
	JGB1741	Inhibition	SIRT1	(Kalle et al. 2010)
	Tenovin-1	Inhibition	SIRT1	(Lain et al. 2008)
	Tenovin-6			
	HR73	Inhibition	SIRT1	(Pagans et al. 2005)
	Cambinol	Inhibition	SIRT1/SIRT2	(Heltweg et al. 2006)
	Salermide	Inhibition	SIRT1	(Lara et al. 2009)
Thiobarbiturate-based inhibitors	Dimethylpyrimidine	Inhibition	SIRT1 and SIRT2	(Uciechowska et al. 2008)
Heterodimeric transcription factor	HIF1α	Activation Inhibition	SIRT3 SIRT6	(Chalkiadaki and Guarente 2015) (Jeong et al. 2014)
Enzymatic inhibitor	GDH	Inhibition	SIRT4	
Protein inhibitor	MYC	Inhibition	SIRT6	
Protein transcription factor	NF-κB	Inhibition	SIRT6	
Cancerous cells	NSCLC cells	Inhibition	SIRT6	(Krishnamoorthy and Vilwanathan 2020)
Signal kinase inhibitor	p-ERK	Inhibition	SIRT6	(Wang et al. 2017)
Cyclin kinase inhibitor	p21Waf1/Cip1	Inhibition	SIRT7	(Lu et al. 2020)
Noncantharidin-paclitaxel compound	NCTD-PTX	Activation	SIRT7	(Wu et al. 2021)
Protein kinase inhibitor	RAS/ERK	Inhibition	SIRT2	(Ding and Hao 2021)
	Ro31-8220	Inhibition	SIRT1/SIRT2	(Trapp et al. 2006)
Splitomicin inhibitor	Benzodeazaoxaflavins	Inhibition	SIRT1/SIRT2	(Rotili et al. 2012)
Indole-based inhibitor	EX527	Inhibition	SIRT1	(Napper et al. 2005)
	AC-93253	Inhibition	SIRT2	(Zhang et al. 2009)
	Inauhzin (INZ)	Inhibition	SIRT1	(Zhang et al. 2012)

Resveratrol-related therapies

Stilbene resveratrol (RSV) is a naturally occurring compound found in grapes, red wine, and certain berries (Beher et al. 2009; Pintea and Rugină, 2019). It exhibits both aging effects and beneficial health impacts associated with calorie restriction. Resveratrol and piceatannol interact with FDL fluorophore structures, binding to SIRT3 and SIRT5

respectively, thereby regulating their activity (Gertz et al. 2012). The modulation of SIRT3 and SIRT5 by resveratrol specifically requires the catalytic domain of the enzyme (Van Damme et al. 2012). The impact of resveratrol on SIRT3 inhibition has not been extensively explored; however, it has dual effects on SIRT5, acting as both an inhibitor and an activator based on substrate interactions (Gertz et al. 2012). Resveratrol having $IC_{50} = 27$ μM caused cell death in Hodgkin-derived cell lines in concentration concentration-dependent manner. However, a lower dose of RSV (25 μM) arrested the S-phase of the cell cycle within 48 h while a high dose (50 μM) caused apoptosis via caspase-3 activation (Frazzi et al. 2013).

4′-Bromo resveratrol demonstrates inhibitory effects on SIRT1 and SIRT3. In crystal structural assays, the nicotinamide C-site and a neighboring site serve as binding sites for the inhibitor. Additional binding sites underscore its importance as a potential target (George et al. 2019). The 2,4-dihydroxyphenyl derivative of piperine RSV was found to be a potent inhibitor of SIRT2 with 78 ± 3% inhibition at only 50 μM concentration while 26 ± 3% at 5 μM concentration (Tantawy et al. 2021). Hirschfeld field surface analysis for intermolecular interaction study investigated that close contact of these derivatives was ascribed to O—H···O bonding. Further docking studies to determine the possible mechanism of inhibition indicated 5b derivative of piperine RSV competes with acyl-Lys substrate and partial occlusion of NAD^+ by closely fitting in the extended C-pocket (Tantawy et al. 2021). SDX-437, distantly related to resveratrol, has led to the discovery of a total of 306 inhibitors that share the common compound SDX-437. These inhibitors exhibit selective inhibitory activity for SIRT3 with 700 nM IC_{50}, having > 100-fold selectivity over SIRT1 (Patel et al. 2015). Novel derivatives of resveratrol have been synthesized to target mitochondria, achieved by linking resveratrol with lipophilic triphenylphosphonium (Biasutto et al. 2008). 1,4-dihydropyridine (DHP) activates SIRT3 (Mai et al. 2009) and honokiol (HKL), a natural biphenolic compound, a DHP-related lignins, also exhibits the potential to activate SIRT3 (Pillai et al. 2015).

Peptides or peptide mimics as inhibitors

Small peptides are designed to specifically target either the polypeptide substrate-binding site or the NAD^+ binding regions of SIRTs as these are very specific, more bioavailable, more stable, non-immunogenic, and fast interacting in nature (Cen 2010). Suramin, for example, inhibits SIRT5 by binding to its NAD^+ binding region, (Schuetz et al. 2007) while it does not exert an effect on SIRT3 and SIRT4 (Loharch et al. 2021). Suramin is a strong inhibitor with $IC_{50} = 297$ nM, 1.15 μM, and 22 μM against SIRT1, SIRT2, and SIRT5 (Hu et al. 2014). Targeting the NAD^+ binding regions is a more appealing strategy for achieving specific inhibition of certain SIRTs. The acyl-Lys binding site serves as a target for inhibiting SIRT5, particularly due to its specific preference for succinyl substrates. Thio-succinylated compounds are also employed to inhibit SIRT5 activity (He et al. 2012). Modifications to the acyl components have led to the development of inhibitors for SIRT5, such as Z-glutaryl CPS1 and 3-methylene 3-phenyl succinyl CPS1 (Roessler et al. 2014). SRT1720, which targets the acetyl-Lys binding site, serves as an inhibitor of SIRT3 (Gertz et al. 2013). Smith and Denu reported trifluroacetyl-lysine peptide as an exceptionally potent inhibitor of SIRTs having $K_{is} = 4.8$ μM and $K_d = 3.3$ μM using Hst2 as SIRT representative in their studies. However, they also reported thioacetyl lysine peptide with Kis = 0.017 μM and $K_d = 4.7$ μM (Smith and Denu 2007). Generally, peptides or peptide analogs-based inhibitors, due to their impermeable and unstable nature, are not appealing for in-vivo or cellular studies. Therefore, non-peptide Nε- tri, tetra, or pentapeptide presented a selective inhibition of SIRT1 in a dose-dependent manner developed; however, replacement of alanine at − 1 and + 1 position of pentapeptide allows to interact with SIRT2.

Bicyclic pentapeptide 10 was found to be an effective inhibitor with $IC_{50} = 0.54$ μM, 0.253 μM, and 0.72 μM against SIRT1, SIRT2, and SIRT3 respectively (Li et al. 2020). A synthetic peptide "YKK (ε-thioAc) AM" with IC50 = 0.13 ± 0.02 μM was reported as a potent inhibitor of SIRT2 (Singh et al. 2021).

Nicotinamide inhibitors

An amide derivative of vitamin B_3 "Nicotinamide" is a non-competitive inhibitor of SIRT1 (Gharote 2024). It presented anti-leukemic effects via potentiating tyrosine kinase inhibitors (TKI) as well as BCR-ABL inhibition. Nicotinamide elevated the sensitivity of doxorubicin and also reduced the cardiotoxicity in CML cell lines (Pan et al. 2020). 6-chloro-2,3,4,9-tetrahydro-1H-carbazole-1- EX-527 cell permeable with IC_{50} as low as 38 nM in vitro whereas 98 nM in vivo exerts its inhibitory effect by disrupting the normal NAD^+-dependent deacetylation mechanism of SIRT1, which is implicated in regulating gene expression, cellular metabolism, and aging-related pathways. This inhibition can lead to altered cellular functions and downstream effects, making EX-527 a valuable tool for investigating the roles of SIRT1–3 with $IC_{50} = 20$ μM, and 49 μM for SIRT2 and SIRT3 respectively in various physiological and pathological contexts (Gertz et al. 2013). However, early reports indicated that EX-527 is more selective for SIRT1 than SIRT2 or SIRT3 as it was shown it was 200- to 500-fold

more effective for SIRT1 (Napper et al. 2005). EX-527 exists in the racemic "S isomer" designated as EX-243 being an active isomer while the "R isomer" designated as EX-242 which inactive form. Being an uncompetitive inhibitor, its IC_{50} values depend on the concentration of NAD^+, the concentration of peptide substrates, and assay conditions (Gertz et al. 2013). GW5074 is another compound known for its inhibitory action on SIRTs, particularly SIRT5. GW5074 interferes with the desuccinylation activity of SIRT5, reducing its effectiveness in removing succinyl groups from target proteins. It is important to note that GW5074 appears to have weaker inhibitory activity when it comes to the deacetylation process commonly associated with other SIRT family members. This specificity highlights the intricate regulation of SIRT activities and the potential for targeted modulation of their functions Titration experiments provided a 19.5 ± 7.3 μM value of IC_{50} of GW5074 for desuccinylation of succprx1 by SIRT5; however, fourfold higher values of $IC_{50} = 97.8 \pm 18.6$ μM for deacetylation of acCPS1 of SIRT5 (Suenkel et al. 2013). Glas and colleagues developed heteroaryl-triayls as potent inhibitors of SIRT5 due to the poor oral bioavailability of the approved drug balsalazide. They reported heteroaromatic, five-membered substitutes, pyrazole, isoxazole, and triazole with $IC_{50} < 10$ μM against SIRT5 (Glas et al. 2022).

ELT-11c is an inhibitor that targets SIRT3, a SIRT with implications for cellular metabolism, aging, and stress responses. SIRT3, like other SIRTs, has a binding site known as the acyl-Lys site, where it interacts with substrates. ELT-11c effectively inhibits SIRT3 with $IC_{50} = 4$ nM by binding to the C-pocket, preventing the enzyme from interacting with its target proteins and performing deacetylation or other related functions. By binding to the acyl-Lys site, ELT-11c interferes with the normal regulatory roles of SIRT3, potentially leading to downstream effects on cellular processes that rely on SIRT3's enzymatic activities (Disch et al. 2013). Overall, these compounds serve as valuable tools for researchers to better understand the intricate roles of SIRTs, which are essential regulators of cellular homeostasis, metabolism, and various disease pathways. However, the tangled SIRT profile of the brain regions of Alzheimer's (AD) and Parkinson's disease patients of both sexes presented the differential NAD^+ dependent deacetylase mechanism directing that valuation of the possibility of promising SIRT-based therapies against neurodegenerative disorders should be contemplated with risk avoidance pointing out further in vivo analysis and clinical studies based on sex dimension (Cartas-Cejudo et al. 2023). By specifically targeting different SIRT family members and their unique mechanisms of action, these inhibitors provide insights into the complex network of SIRT-mediated processes within cells.

Conclusion

The fascinating field of SIRTs and their modulation presents a diverse landscape of potential therapeutic interventions and mechanistic insights into cellular processes. Through extensive structural and mechanistic investigation, it has been revealed that SIRTs, such as SIRT1-5, are critical players in a wide range of biological processes. The intricate balance between their deacetylation, desuccinylation, and other enzymatic activities has been linked to cell survival, proliferation, apoptosis, and cellular metabolism. Furthermore, the modulation of SIRT activities by natural compounds, synthetic inhibitors, and activators has paved the way for innovative therapeutic strategies targeting rare and common diseases which were of considerable importance. Notably, the recent discoveries surrounding SIRT-specific inhibitors and activators have allowed researchers to delve deeper into understanding the precise mechanisms underlying their functions. Compounds like MHY2256, pyrazolone, AGK2, and ELT-11c have provided valuable tools to selectively inhibit or enhance the activities of specific SIRT family members. This knowledge has enabled researchers to dissect the roles of individual SIRTs and their interactions with various cellular substrates, shedding light on complex regulatory networks. However, the intricate nature of SIRT functions also underscores the need for cautious consideration when designing interventions, ensuring that the delicate balance of cellular processes is maintained. In conclusion, the study of SIRTs opens new avenues for unraveling the complexities of cellular regulation, as well as helps to validate SIRT as a potential prognostic and diagnostic marker for large populations. The discoveries made in this field not only contribute to our fundamental understanding of biology but also hold the promise of groundbreaking therapies that could revolutionize the way we approach various health challenges in the future. As research continues to advance, we anticipate that the insights gained from studying SIRTs will lead to transformative discoveries with far-reaching implications for human health and well-being.

Authors contributions Shagufta Kamal and Sharon Babar: writing-original draft. Kanwal Rehman and Shagufta Kamal: investigation, conceptualization, writing-final draft, and editing. Muhammad Sajid Hamid Akash and Kanwal Rehman: supervision, conceptualization, methodology. Amjad Hussain and Waqas Ali: literature search. The authors confirm that no paper mill and artificial intelligence was used.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval N/A.

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