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Sirtuin-3 (SIRT3) and the Hallmarks of Cancer

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Abstract

Sirtuins (SIRT1-SIRT7), the mammalian homologs of the silent information regulator 2 (Sir2) in *Saccharomyces cerevisiae*, have been a major focus of study in the scientific community this past decade because of their emerging role in cancer biology and other age-related diseases. Emerging functions for this unique family of enzymes include roles in genomic stability, angiogenesis, metabolism, and anoikis. Here, we review recent developments on the role of sirtuins in cancer with a particular focus on SIRT3 and its role in the hallmarks of cancer and as a potential drug target for cancer treatment.

Keywords: sirtuin-3, SIRT3, sirtuins, cancer, tumor promoter, tumor suppressor, anoikis

Introduction

Cancer is one of the leading causes of death worldwide.[1] Despite advances in treatment, outcomes have not improved significantly. This highlights the importance of exploring new areas of investigation to effect change and curtail this devastating disease.

Sirtuins (SIRT1-SIRT7), the mammalian orthologs of the silent information regulator 2 (Sir2) in *Saccharomyces cerevisiae*, have been a major focus of study in the scientific community this past decade in part because of their emerging role in cancer biology.[2-4] This evolutionarily conserved family of proteins works as NAD-dependent deacetylases or ADP-ribosyltransferases.[5,6] Different sirtuins are located in different subcellular compartments and can thereby modulate different targets in the cell, which may explain their important role in tumorigenesis.[3,7] An important member of this family that appears to be a critical modulator of tumorigenesis is sirtuin-3 (SIRT3).[7] In a previous review,[7] we discussed the dual role of SIRT3 in cancer, where we highlighted its role in cell survival, apoptosis, and metabolism in regards to cancer biology.[7] The aim of the current review is to highlight recent developments in the role of sirtuins in cancer biology with a particular focus on SIRT3 and its role in the hallmarks of cancer (Figure 1) and as a potential drug target for cancer treatment.

Sirtuins and Cancer: An Overview

Cancerous cells possess 6 hallmarks that include self-sufficiency in growth signals, insensitivity to antigrowth signals, apoptosis evasion, sustained angiogenesis, limitless replicative potential, and tissue invasion and metastasis.[8] Additional characteristics that have recently emerged include dysregulation of cellular energy, avoidance of immune distraction, genomic instability, and tumor-promoting inflammation. These features define the myriad of dysregulated cancerous cell attributes.[9] Interestingly, growing evidence supports an important role for sirtuins in these cancer hallmarks. However, it is important to keep in mind that several sirtuins exhibit a dual role in tumorigenesis.[7] Understanding the mechanisms that regulate this duality is critical to developing sirtuin-based anticancer therapeutics.

In this review, we discuss the different molecular and cellular transitions that cancerous cells undergo and highlight the current evidence that sirtuins, and specifically SIRT3, can modulate these processes and thereby affect the outcome of tumorigenesis.

SIRT3 and Genomic Instability

The 6 hallmarks of cancer[8] are acquired directly or indirectly via several "hits" or mutations on the DNA that lead to genomic instability.[9-12] These multiple "hits," as stated by Knudson's[13] hypothesis or the mutator phenotype hypothesis,[14,15] can result from chronic exposure to carcinogens, such as tobacco, alcohol, or viruses such as HPV.[16] These mutations may result in the amplification of oncogenes or inactivation of tumor suppressors.[15,16] In addition, the multistep model of cancer also demonstrates that normal cells must undergo several genetic and cellular changes to become cancerous cells.[11]

Direct links between sirtuins and genomic stability have been demonstrated, primarily via a genetic approach. Mice lacking SIRT1 exhibit genomic instability, impaired DNA damage response, and tumorigenesis.[17] Similarly, SIRT2 functions as a G2 checkpoint mitotic regulator, thus preventing chromosomal instability, and it might also function as a tumor suppressor.[18-20] SIRT6-deficient mice also show signs of

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genomic instability and an aging-like phenotype.[21] In the case of SIRT3, direct evidence for its role in genomic instability has not been as forthcoming, especially given that most studies support the concept that SIRT3 is primarily mitochondrial in its localization.[22-29] SIRT3-null mice appear to have normal development and fertility.[23,30] However, recently, Kim *et al.*[31] demonstrated that mouse embryonic fibroblasts (MEFs) from SIRT3 knockout mice exhibit abnormal mitochondrial physiology, increased stress-induced superoxide levels, and genomic instability. Additionally, these mice develop ER/PR-positive mammary tumors over a 24-month observation period, suggesting a tumor suppressor role for SIRT3 in this cancer type.[31] Mechanistically, SIRT3-mediated regulation of reactive oxygen species (ROS) may be the path regulating genomic instability. Since SIRT3 seems to regulate ROS through Mn-SOD and SOD2 modulation,[32,33] and because increased ROS levels have been associated with mutagenesis promotion and genomic instability,[34] these studies suggest an indirect role for SIRT3 in controlling genomic stability.[4] Additional studies that support nuclear localization for SIRT3 upon cellular stress suggest that the histone modifications H4K16Ac and H3K9Ac are targeted by SIRT3,[35] thus introducing the possibility that SIRT3 might also play a direct regulatory role in controlling genomic stability.

SIRT3 Controls the Limitless Replicative Potential of Cancer Cells

Normal cells become senescent after a defined number of cell doublings because of their limited capacity for replication.[36,37] Cancerous cells, in contrast, can perpetually maintain their telomere lengths during replication, possess limitless replication potential, and are known to be immortalized.[37] Telomeres are essential for chromosomal protection and function and shorten after each cell division. The enzyme telomerase maintains telomeric length during cell replication.[38] Human telomerase reverse transcriptase (hTERT) creates single-stranded DNA using single-stranded RNA as a template. Upregulated levels of hTERT are a common feature of all tumors.[39,40]

Evidence supports a role for both SIRT1 and SIRT6 in telomere function in part because of their nuclear localization.[41-43] Inhibition of SIRT1 is associated with enhanced telomerase activity in human cells, such as HeLa cells.[43] Whether this can be demonstrated in other cell types or whether this contributes to the immortalization of tumors has yet to be determined. However, there seems to be a direct link between SIRT1, telomerase function, and tumorigenesis. SIRT6 also seems to be important in maintaining telomeric function. Downregulation of SIRT6 activity results in telomere dysfunction and end-to-end chromosomal fusions.[42] In addition, SIRT6-deficient cells show an increased susceptibility to genotoxic DNA damage, resulting in the accumulation of chromosomal abnormalities and genomic instability.[21] Because most reports support mitochondrial localization for SIRT3, no information has yet been reported that links SIRT3 to telomeres and telomeric functions. However, the data by Kim *et al.*[31] support that SIRT3 knockout in MEFs creates a transformation-permissive phenotype that allows immortalization in the presence of oncogenic hits with Myc or Ras. Whether this event is linked to telomeric function is a question that needs to be explored.

SIRT3 Controls Proliferative and Survival Signaling

Cell proliferation is controlled in normal cells by the production and release of proliferative and antiproliferative signals. Therefore, maintaining the balance between both proliferative and antiproliferative signaling processes is essential. However, this balance is tipped toward the production and release of uncontrolled proliferative signals that cannot be regulated by the antiproliferative signals in cancer cells.[9] Several studies highlight a prosurvival role for SIRT3 in both normal and cancer cells/tissues under different cellular conditions,[33,44-54] thus supporting a tumor promoter role for SIRT3 in cancer. Hence, SIRT3 seems to control proliferative and survival pathways in certain cell/tissue types, including oral cancer, breast cancer, cardiomyocytes, HEK293 cells, and neurons, although the exact mechanisms by which SIRT3 exerts these roles are still not fully understood.

SIRT3 contributes to cell proliferation and survival by different mechanisms. The role of ROS in cancer cell biology is well established. ROS plays an important role in transformation to a tumorigenic phenotype.[55,56] However, normal cells also require low levels of ROS for normal physiological functions. Thus, normal cells possess lower ROS levels compared to cancer cells.[57,58] ROS can modulate both cell survival and apoptotic pathways.[59,60] SIRT3 regulates ROS levels in normal and cancer cells. In the subset of cancers in which SIRT3 is overexpressed, such as head and neck squamous cell carcinoma (HNSCC),[44] SIRT3 maintains ROS levels at the appropriate level for maintaining a proliferative and aggressive phenotype, thus promoting tumorigenesis and preventing apoptosis. In HeLa cells, SIRT3 deacetylates Ku70, which augments Ku70-Bax interactions and prevents Bax translocation to the mitochondria, thus protecting these cells from genotoxic and oxidative stress-mediated cell death and promoting cell survival.[46] In cardiomyocytes, SIRT3 suppresses ROS via the activation of a FOXO3a-dependent antioxidant mechanism via modulation of the MAPK/ERK and PI3K/Akt proliferation signaling pathways[49] and via activation of NF-κB.[61] Furthermore, SIRT3 exerts a neuroprotective role in Huntington disease by modulating the AMP kinase pathway.[62] Hypoxia-inducible factors (HIFs) mediate cellular responses to hypoxia and directly activate the transcription of genes involved in tumorigenesis, including vascular endothelial

growth factor (VEGF) and transforming growth factor α (TGF-α).[63] Under hypoxic conditions, SIRT3 overexpression inhibits ROS production, glycolysis, proliferation, and HIF-1α stabilization and its downstream transcriptional activity, thus decreasing tumorigenesis.[64,65] In summary, these pathways are commonly dysregulated in several cancer types. Given that SIRT3 controls these multiple pathways supports the concept that SIRT3 is positioned to regulate tumorigenesis.[63,66-69]

SIRT3, Apoptosis, Cell Death, and Growth Suppression

A proapoptotic role has also been advanced for SIRT3 in some normal and cancer cell types.[31,64,65,70-74] This dual role for SIRT3 in normal and cancer cells has been discussed in detail in our previous review.[7] Briefly, we reported that SIRT3 promotes survival and protects several cell types from cellular damage by maintaining mitochondrial integrity and functions and by enhancing their resistance to stress-mediated cell death, where ROS regulation is central to these processes. Apoptotic cell death and growth suppression pathways seem to be regulated by additional signaling pathways that include JNK, Bax, HIF-1α, but also ROS.

Recent evidence continues to support this dual role for SIRT3. The tumor suppressor p53 is commonly mutated in most cancer types.[75,76] In bladder cancer, SIRT3 deacetylates p53, thus abrogating growth arrest and cellular senescence and supporting a prosurvival role for SIRT3.[53] In contrast, in hepatocellular carcinoma, SIRT3 levels are downregulated. Thus, SIRT3 seems to prevent p53 degradation by reducing the activity of the negative regulator Mdm-2 on p53.[74] Interestingly, a recent report supports that SIRT3 as well as SIRT2, SIRT6, and HDAC3 are all correlated with the overall survival of chronic lymphocytic leukemia patients. However, a poor prognosis was associated with the overexpression of HDAC7 and HDAC10 but the underexpression of HDAC6 and SIRT3.[77] Furthermore, SIRT3 enhances growth arrest and apoptosis in several osteosarcoma and colorectal carcinoma cells and in noncancer human cell lines such as lung and retinal epithelial cells.[70] This action is mediated, at least in part, by SIRT3 modulation of the JNK2 signaling pathway in these cell lines.[70]

SIRT3, Metabolism, and Cancer

The role of SIRT3 in metabolism and tumorigenesis has been extensively discussed.[4,78,79] Furthermore, it is important to highlight that altered tumor metabolism is one of the emerging hallmarks of tumorigenesis.[9] In recent work, SIRT3 was found to be an important regulator of the Warburg effect. SIRT3 mediates metabolic reprogramming by destabilizing HIF-1α, which regulates glycolytic gene expression. Specifically, loss of SIRT3 increases ROS production, and this leads to HIF-1α stabilization. In breast cancers, SIRT3 expression is reduced, and its loss is correlated with the upregulation of HIF-1α target genes. Furthermore, SIRT3 overexpression suppresses glycolysis and proliferation in breast cancer cells, suggesting a metabolic mechanism for tumorigenesis.[78,79] In another report, SIRT3 was found to suppress HIF-1α and tumor growth by inhibiting ROS production. Thus, since metabolism and the mitochondria play a major role in tumorigenesis, and SIRT3 regulates metabolism within the mitochondria, SIRT3 is pivotally located to balance the metabolic targets that control several age-related diseases including cancer. This implicates SIRT3 as a potential target to prevent and treat these diseases.

SIRT3 and Angiogenesis

Angiogenesis facilitates cancer development and progression.[80] The association between sirtuins and angiogenesis has been well established for SIRT1. SIRT1 is highly expressed during blood vessel formation.[81] Downregulation of SIRT1 function blocks sprouting angiogenesis and branching morphogenesis of endothelial cells, thus resulting in the downregulation of genes, such as FOXO1, that are involved in blood vessel development and vascular remodeling.[81] In addition, endothelial cell–specific deletion of SIRT1 in mice blunts ischemia-induced neovascularization in the hindlimb.[81] In agreement with this report, activation of SIRT1 by resveratrol *in vivo* resulted in increased capillary density via VEGF and nitric oxide synthase upregulation 3 weeks after myocardial infarction.[82] Another important angiogenic factor is HIF-1. HIF-1 seems to activate SIRT1 under hypoxic conditions, and SIRT1 selectively augments HIF-2 signaling during hypoxia, indicating a link between HIF and SIRT1 signaling during hypoxia.[83] Moreover, SIRT1 deacetylates and inactivates p53, a proapoptotic and antiangiogenic factor, thereby mediating a cardioprotective role and suggesting that SIRT1 modulation of p53 may be a mechanism by which SIRT1 controls angiogenesis.[84,85]

To our knowledge, there are no reports demonstrating a direct role for SIRT3 in the regulation of angiogenesis. However, as mentioned above, an association between SIRT3 and both HIF-1α and p53 has been reported.[53,64,65] SIRT3 partially abrogates p53 activity to enact growth arrest and senescence in a bladder carcinoma cell environment.[53] Loss of SIRT3 also increases ROS production and HIF-1α stabilization. Thus, when SIRT3 expression is reduced, such as in human breast cancers, its loss is associated with the upregulation of HIF-1α target genes.[64] Similar effects are also noted in human colon carcinoma and osteosarcoma cells.[65] Thus, SIRT3 stable knockdown results in enhanced tumorigenesis in a xenograft model and augmented HIF-1α protein stability and transcriptional activity.[65] Although these reports did not investigate angiogenesis in these cancer types, their results support an opposite effect on HIF-1α by SIRT3 compared to SIRT1 and, by extension, an opposing role in angiogenesis. In contrast, the role of SIRT3 on p53 seems consistent with that of SIRT1 since both can deacetylate and inactivate p53 transcripts, thus promoting cell

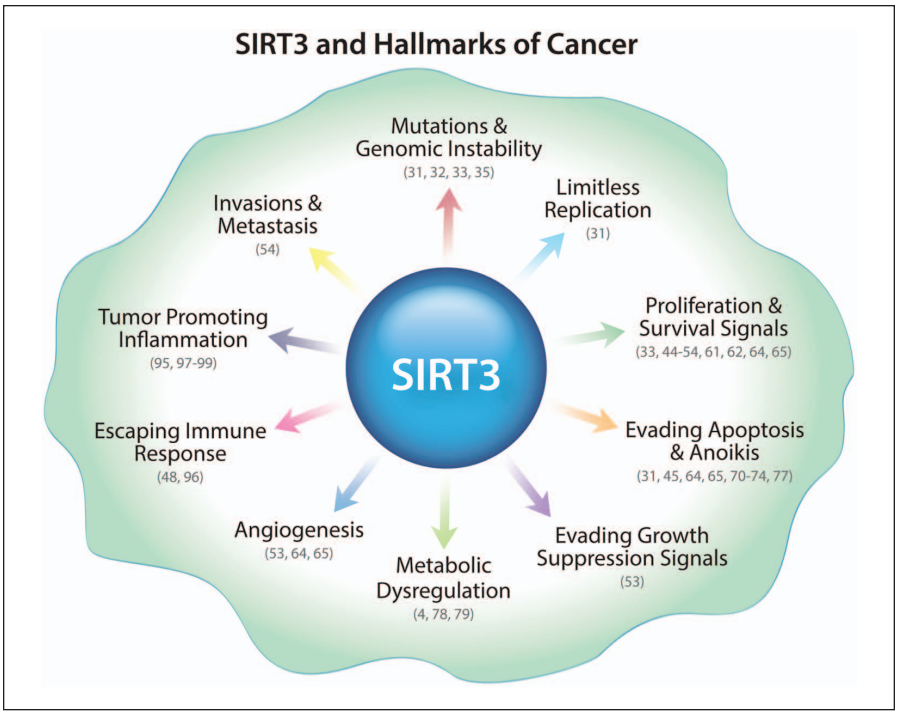

Figure 1. Mutations and genomic instability: Genomic instability and mutations may result in the amplification of oncogenes or inactivation of tumor suppressors, which drive tumor progression. SIRT3 promotes mutagenesis and increases genomic stability through ROS and deacetylation of H4K16ac and H3K9ac.[31-33,35] Limitless replication: Normal cells have a limited life span, whereas cancer cells possess infinite replicative potential, also called cell immortalization. SIRT3 is involved in the immortalization process in the presence of Myc or Ras.[31] Proliferation and survival signals: Cancer cells become self-sufficient in growth signals and therefore acquire uncontrolled proliferative capacity. SIRT3 plays a role in proliferative and survival signaling pathways in normal and cancer cells (tumor promoter) via maintaining ROS thresholds, activation of a FOXO3-dependent antioxidant mechanism and NF-κB, and its modulation through MAPK/ERK, PI3K/Akt, and AMP kinase pathways.[33,44-54,61,62,64,65] Evading apoptosis and anoikis: Apoptosis, a form of programmed cell death, is a genetically regulated cell-suicidal mechanism involved in the regulation of normal tissue homeostasis. However, cancer cells are able to bypass this mechanism. In addition to regulating cell proliferation and survival, SIRT3 plays a proapoptotic role (tumor suppressor) in normal and cancer cell types.[31,64,65,70-74,77] Anoikis resistance or anchorage-independent growth contributes to cancer development and progression. SIRT3 plays a role in mediating anoikis resistance and tumorigenesis.[45] Evading growth suppression signals: Cancer cells negatively regulate cell proliferation, and many of these programs depend on the actions of tumor suppressor genes. p53-induced growth arrest is regulated by the mitochondrial SIRT3 deacetylase.[53] Metabolic dysregulation: Cancer cells have developed the ability to reprogram their cellular metabolism to sustain growth and tumor progression. SIRT3 modulates cellular metabolism, the Warburg effect, and tumorigenesis.[4,78,79] Angiogenesis: To sustain the growth of tumors, cancer cells chronically activate angiogenesis and an unbalanced mix of proangiogenic signals. SIRT3 is indirectly associated with angiogenesis through HIF-1α and p53.[53,64,65] Escaping immune response: Cancer cells acquire the ability to evade immunological destruction, especially by T and B lymphocytes, macrophages, and natural killer cells. SIRT3 is involved in inflammation and autoimmune dysfunction through activation of the renin-angiotensin system.[48,96] Tumor-promoting inflammation: Innate immune cells, which are designed to fight infections and heal wounds, inadvertently support these cancer hallmarks, thereby leading to tumor promotion. SIRT3 is involved in proinflammatory responses through the modulation of ROS.[95,97-99] Invasion and metastasis: Cancer cells invade local tissue, spread to distant sites, and develop new tumors at secondary sites. Increased levels of SIRT3 transcription are associated with lymph node metastasis in breast cancer.[54]

survival. Therefore, one may expect a proangiogenic role for SIRT3, at least in bladder carcinoma,[53] but not in breast and colon carcinoma and osteosarcoma,[64,65] based on the current reports. Additional studies are needed to establish a clear understanding of the role of SIRT3 in angiogenesis.

SIRT3, Inflammation, and the Immune Response

Growing evidence indicates that inflammation contributes to tumor formation by modulating the tumor microenvironment.[9,86,87] Several sirtuin members, including SIRT1, SIRT6, and SIRT7, are involved in inflammation.[88,89] Most of these studies support an inhibitory effect of these sirtuins on inflammation. For instance, SIRT1 deacetylates the RelA/p56 subunit of NF-κB, a transcription factor involved in inflammation, and thereby attenuates its downstream signaling cascades and inflammation.[90] Similarly, SIRT6 attenuates NF-κB signaling at the transcriptional level.[91] Both SIRT1- and SIRT7-null mice demonstrate autoimmune-like conditions and the development of inflammatory cardiomyopathy.[92] In addition, SIRT6 appears to play a role in inflammation by enhancing the proinflammatory cytokine expression of TNF-α and IL-6 in innate and adaptive immune cells by modulating NAD cellular levels via Nampt enzymatic activity.[93]

The link between mitochondrial functions, inflammation, and cancer has been well documented in lung and colorectal cancers.[94] SIRT3 positively regulates antioxidant gene expression, thus decreasing ROS accumulation in tubulointerstitial lesions in proteinuric kidney disease, thereby leading to decreased inflammation.[95] In addition, activation of the renin-angiotensin system, ACE/Ang II/AT1R, is associated with downregulation of the prosurvival genes Nampt and Sirt3, increase in ROS production, and proinflammatory cytokine and chemokine release, leading to cell senescence, inflammation, and the development of autoimmune dysfunctions.[48,96] Moreover, SIRT3 is a key effector of neutrophil and lymphocyte immune responses after exercise. Thus, a regulatory role for SIRT3 in inflammatory pathways appears plausible.[97,98] In aggregate, although direct evidence for an association between SIRT3,

inflammation, and cancer does not yet exist, there is supporting evidence suggesting that these events may work in concert; this is an area that remains to be explored.

SIRT3, Invasion, and Metastasis

The multistep model of cancer states that the accumulation of genetic alterations precedes the onset of cancer. These mutations become phenotypically translated at the cellular level to ultimately reach an end point of invasion and metastasis. This final step involves the loss of cell-to-cell and cell–to–extracellular matrix (ECM) adhesion, loss of basement membrane adhesion, and survival of tumor cells in the bloodstream to reach and colonize new metastatic sites.[9] The role of several sirtuins has been demonstrated in invasion and metastasis. SIRT1 expression levels correlate with tumor stage, lymph node metastasis, tumor invasion, and shorter overall survival in gastric carcinoma patients.[99] In addition, SIRT1 downregulation attenuates prostate cancer cell migration and invasion, suggesting that SIRT1 may be a promising target to prevent the metastasis of prostate cancer.[100] Ashraf *et al.*[54] reported that SIRT3 transcription levels are associated with lymph node–positive metastatic breast cancer. These studies indicate an association between SIRT1 and SIRT3 levels and the aggressiveness and progression of these cancer types.

SIRT3 and Anoikis

Apoptosis resulting from the loss of cell adhesion or inappropriate adhesion to the ECM is defined as anoikis.[101] Resistance to anoikis contributes to the development and progression of cancer. Anoikis resistance and anchorage independency allow tumor cells to invade adjacent tissues and organs as well as metastasize to lymph nodes and other distant sites. Thus, understanding the mechanisms that regulate anoikis resistance is important for counteracting tumor progression and preventing metastasis.

We reported that anoikis activates the CD95/Fas-mediated signaling pathway that is regulated by receptor-interacting protein (RIP), a kinase that shuttles between Fas-mediated cell death and integrin/focal adhesion kinase (FAK)–mediated survival pathways.[102] RIP seems to play a dual role in these processes since it can bind to FAK in human tumor cells, providing a prosurvival signal, and it interacts with Fas in cell death pathways to initiate anoikis.[102-104] Therefore, RIP participates in both prosurvival and cell death pathways and thus constitutes a possible target for modulating anoikis. Because SIRT3 also regulates cell survival, apoptosis, and tumorigenesis,[7,44] the authors hypothesized that SIRT3 might engage in cross-talk with Fas/RIP/FAK death-survival pathways in cancer cells. Indeed, we showed that SIRT3 mediates anoikis resistance in oral cancer and its negative relation with RIP expression.[45] We further demonstrated that RIP likely negatively regulates SIRT3 in anoikis resistance, and an anoikis-resistant orasphere phenotype defined by higher SIRT3 and low RIP expression contributes to a more aggressive phenotype in oral squamous cell carcinoma (OSCC) development. Multiple studies have supported the concept that spheroid formation promotes cancer cell survival and tumorigenesis.[105-107] In addition, SIRT3 localizes to the mitochondrial matrix, and RIP can localize to the mitochondrial outer membrane,[108,109] suggesting that these 2 molecules may interact indirectly through other molecules in the context of anoikis resistance. One putative molecule would be cyclophilin D. RIP appears to negatively regulate cyclophilin D, thus inducing mitochondrial-mediated cell death.[108] In addition, SIRT3 interacts with and deacetylates the regulatory component of the mitochondrial permeability transition pore, cyclophilin D.[50] These data support the idea that RIP and SIRT3 play opposite roles in regulating cell death and survival through a common third molecule, such as cyclophilin D. Furthermore, evidence suggests that RIP regulates ROS-mediated signaling,[110,111] and RIP and SIRT3 may be functionally related through ROS regulation pathways in the context of anoikis resistance.

SIRT3's Dual Role in Cancer

Several sirtuin family members play a dual role in tumorigenesis. This duality primarily relates to SIRT1 and SIRT3[7,112-114] and may result from tissue and tumor type–specific function. In addition, the cellular microenvironment, whether under normal or cellular stress conditions, may play an important role in determining this dual function. More studies are needed to explore this complex role of SIRT3 in different cancer types and under different cellular conditions to clearly determine under which conditions SIRT3 functions as a tumor promoter versus a tumor suppressor.

SIRT3 as a Potential Therapeutic Target for Cancer: What Does the Future Hold?

Sirtuins are linked to age-related diseases including diabetes, hearing loss, and cancer. Hence, it is surmised that these diseases usually share common pathways. An advantage to developing novel and specific modulators of sirtuins might allow the treatment of several age-related diseases using a common drug. However, the mechanism of action of such drugs and their off-target effects would have to be clearly identified. For instance, in the case of a proposed tumor suppressor effect for SIRT3 in human colon carcinoma and osteosarcoma,[65] the SIRT3 activator would enhance the tumor suppressor effect of SIRT3 in this cancer type and would reduce ROS production. However, because of the reported dual role of sirtuins, including that for SIRT1 and SIRT3, such therapies could be met with potential unwanted side effects. A big concern would be the potential promotion of other different cancer types, given the opposing roles of SIRT3 in breast and head and neck cancer. However, with the discovery of unique biomarkers for each

cancer type, the development of effective personalized cancer therapy with proper and novel targeted therapies, and delivery systems to the specific sites of interest, this issue or concern could be minimized. Thus, personalized therapy may allow us to better screen patients for the best modality of treatment to achieve better outcomes.

Several inhibitors of sirtuins have been developed and tested *in vitro*,[44,115-118] but few have been tested *in vivo* for the treatment of age-related diseases, including cancer.[119,120] However, a SIRT1 activator, resveratrol, has been tested in ongoing clinical trials for treating different age-related diseases.[121,122] To our knowledge, there are no reported clinical trials on modulating sirtuin activity for cancer therapy.

In summary, the use of sirtuin activators/inhibitors is still in an early stage of development. Whether sirtuin modulators will deliver as novel anticancer agents is yet to be determined. However, the data accumulated thus far suggest some interesting leads and opportunities in this rapidly developing field.

Concluding Remarks

Sirtuins are emerging as a unique family of enzymes playing critical regulatory roles in genomic stability, metabolism, angiogenesis, and anoikis. The dual role of sirtuins in cancer development highlights the importance of understanding their biological mechanisms of action in each tumor to determine whether inhibition or activation might be of therapeutic value.

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