Deacetylation by SIRT1 Reprograms Inflammation and Cancer

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Abstract

NAD⁺-dependent deacetylase SIRT1 is a master regulator of nucleosome positioning and chromatin structure, thereby reprogramming gene expression. In acute inflammation, chromatin departs from, and returns to, homeostasis in an orderly sequence. This sequence depends on shifts in NAD⁺ availability for SIRT1 activation and deacetylation of signaling proteins, which support orderly gene reprogramming during acute inflammation by switching between euchromatin and heterochromatin. In contrast, in chronic inflammation and cancer, limited availability of NAD⁺ and reduced expression of SIRT1 may sustain aberrant chromatin structure and functions. SIRT1 also influences inflammation and cancer by directly deacetylating targets like NFκB p65 and p53. Here, we review SIRT1 in the context of inflammation and cancer.

Keywords: SIRT1, chromatin regulation, NFκB, inflammation, cancer

Introduction

Posttranslational acetylation/deacetylation modifications of histone and non-histone proteins are primary modifiers of many physiological processes.¹ Histone acetyltransferases (HATs) add acetyl groups to histone lysine residues, significantly reducing their electrostatic attraction to the negatively charged DNA backbone and rendering chromatin DNA more accessible to RNA polymerase II for completing gene transcription.² Histone deacetylases (HDACs I, II) counteract the HAT effect by removing acetyl groups and, by restoring a more compact chromatin structure, silencing genes. The physiological significance of acetylation/deacetylation of nonhistone proteins varies with substrate properties and locations.³ For example, HDACs deacetylate cytoplasmic STAT1 and STAT3 and interrupt their signal transduction, while HDACs deacetylate nuclear p53-repressing apoptosis in response to DNA damage.⁴⁻⁷

Over the past 2 decades, another deacetylase class, the yeast silent information regulator 2 (Sir2) family,

emerged as energy sensors that control many cellular processes during stress and aging.⁸ Through a unique catalytic mechanism, they modify both histone and nonhistone substrates: their deacetylase activity depends on nicotinamide adenine dinucleotide (NAD⁺) but not response to HDAC inhibitor trichostatin A⁹; some members of the family also modify targets by ADP ribosylation. Therefore, the Sir2 family is referred to as a class III histone deacetylase and is distinct from classic HDACs.

There are 7 Sir2 mammalian homologs, sirtuins, termed SIRT1 through SIRT7.¹⁰ SIRT1, the focus of this review, is the best characterized. Its structure is distinct from the others; it has the unique ability to translocate freely among subcellular compartments and deacetylate broad heterogeneous substrates. These biochemistry properties explain its extensive regulatory roles in physiological and pathophysiological activities related to gene transcription, circadian rhythm, longevity, metabolism, inflammation, and cancer.^{11,12}

Inflammation and cancer are related pathophysiological processes. Epide-

miological studies support that most cancers are linked to acquired somatic mutations, environmental factors, infection, and inflammatory diseases. Chronic infections, inflammatory disease, and obesity each contribute up to 20% of all cancers.¹³⁻¹⁵ Such a prominent link suggests a molecular connection between cancer and inflammation.^{16,17} The inflammatory process, while protective, induces oxidative damage, DNA mutations, angiogenesis, and other changes conducive to cell transformation and cancer growth.¹⁸⁻²⁰ Accumulated data demonstrate that acetylation/deacetylation modifications of histone and non-histone proteins play key roles in

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regulating the gene expression of inflammatory mediators and contribute to inflammation-induced carcinogenesis.^{21,22} Recently, the NAD⁺-dependent deacetylase SIRT1 has been implicated in the progression of inflammation to cancer.²³⁻²⁵

SIRT1 Structure and Function

Human SIRT1 consists of 747 amino acids, divided into 4 major regions: N-terminal domain (residues 1-182), allosteric site (residues 183-243), catalytic core (aa 244-498), and C-terminal domain (aa 499-747).²⁶ The N- and C-terminal domains are non- α , non- β structure regions. These disordered segments of SIRT1 act as flexible linkers with its specific substrate proteins. Anchor analysis predicts that human SIRT1 contains 14 disordered binding regions for distinct substrates. In addition, the N- and C-terminals are required for SIRT1 activity. SIRT1 mutants truncated by the deletion of either the N- or C-terminal fail to catalyze the deacetylation reaction and attenuate the inhibitory potency of EX527, Ro 31-8220, and nicotinamide (NAM) in SIRT1-catalyzed H3(4-14)K9Ac peptide deacetylation.²⁷ Especially, a 25-amino acid sequence (aa 631-655) at the C-terminal is essential to SIRT1 activity.²⁸ Two nuclear-leading and two nuclear-exporting sequences in the N-terminal region are crucial because they allow SIRT1 to translocate freely between the nucleus and cytoplasm to meet SIRT1 requirements in different physiological and pathophysiological settings.²⁹

SIRT1 catalyzes the protein deacetylation reaction in its catalytic core, which consists of 2 subdomains for NAD⁺ and substrate binding.^{26,30} NAD⁺ binds to a specific pocket of two hydrophobic patches at the subdomains' interface. Acetylated substrate binds to a small zinc domain next to the NAD⁺ binding site. NAD⁺ binding changes the catalytic core's secondary structure to increase substrate protein access. This revised structural arrangement ensures that catalysis of protein deacetylation by

SIRT1 is NAD⁺ dependent and proceeds as a sequential biochemical reaction, initiated by NAD⁺ binding to the catalytic core. NAD⁺ carries the acetyl group and yields 2'-O-acetyl-ADP ribose and NAM.^{9,31,32} Sirtuin inhibitors, such as EX₅₂₇ (specific for SIRT1) and NAM, compete with NAD⁺ for the NAD⁺ binding site,³³ while DBC1 (deleted in breast cancer 1) competes with acetylated proteins for the small zinc site to inhibit SIRT1's catalytic activity.³⁴ Next to the N-terminal in the catalytic core is the compacted allosteric domain, which positively regulates sirtuin activity. A small nuclear protein active regulator of sirtuin (AROS) and SIRT1 activators, such as resveratrol, bind to the allosteric site and stimulate SIRT1-dependent p53 deacetylation.^{35,36}

SIRT1 plays well-documented regulatory roles in such diverse cellular processes as chromatin structure, gene transcription, metabolism, circadian rhythm, and inflammation.¹¹ It can perform so many physiological functions due to its broad substrates and unique property of free translocation among subcellular compartments. Basically, two groups of acetylated proteins are its targets: histone and nonhistone proteins.³⁷ The acetylation/deacetylation status of histone proteins determines whether chromatin is accessible for gene transcription (AROS). SIRT1 actively deacetylates H1K26, H3K9, and H4K16 and facilitates chromatin DNA compaction, silencing gene transcription.^{9,38} In contrast, nonhistone substrates of SIRT1 are generally the molecules or enzymes that control signal transduction, metabolism, or gene transcription. Their diverse protein properties and cellular locations enable SIRT1 to play dual regulatory roles in different cellular processes or different phases of a certain process.^{37,39} For example, SIRT1 deactivates proinflammatory gene expression by deacetylating NF κ B/p65 but stimulates anti-inflammatory gene expression by targeting RelB and PGC-1 α during acute inflammation.⁴⁰ At the substrate level, SIRT1 inhibits apoptosis by deacetylating p53 but stimulates fatty acid

synthesis by deacetylating acetyl CoA synthase 1.⁴¹⁻⁴⁴

This broad SIRT1 bioactivity is coordinated through precise regulation of deacetylating catalysis, transcription, translation, and stabilization. Specific binding sites allow SIRT1 activators/inhibitors to manipulate the intensity of deacetylase activity, but NAD⁺ availability is the primary measure of SIRT1 activation. The NAD⁺/NADH ratio determines SIRT1 translocation between subcellular compartments: more NAD⁺ attracts and activates SIRT1, while negative feedback from the NAD⁺-hydrolyzed product NAM inhibits SIRT1 activity by competing for NAD⁺ binding sites in the catalytic core.⁴⁵ Thus, the enzymes nicotinamide phosphoribosyltransferase (NAMPT)^{46,47} and nicotinamide mononucleotide adenylyltransferase (NMNAT)^{47,48} in the NAD⁺ salvage pathway and indoleamine 2,3-dioxygenase⁴⁹ in the kynurenine NAD⁺ synthesis pathway play key roles in SIRT1 activation by both increasing the NAD⁺ level and decreasing the NAM level. Note that NAD⁺ also serves as a cofactor for many dehydrogenases in metabolic pathways, so cellular metabolism is regulated by SIRT1 activity. Fasting or calorie restriction increases NAD⁺ and stimulates SIRT1 activation; high levels of reducing agent NADH limit SIRT1 activation.^{50,51}

SIRT1 gene expression is tightly controlled by positive feed-forward and negative feedback loops; E2F1-SIRT1-E2F1 and HIC1-SIRT1-p53 are two representative regulatory loops.^{52,53} DNA damage induces the expression of transcription factor E2F1, which enhances the gene transcription of SIRT1 and several apoptotic proteins. In turn, SIRT1 deacetylates E2F1, deactivates its transactivation activity, and attenuates its own gene expression. Hypermethylated in cancer 1 (HIC1) is a sequence-specific transcription repressor that interacts with corepressor CtBP and HDAC1 to inhibit the transcription of SIRT1 and a panel of oncogenes. p53 activates HIC1 gene transcription; SIRT1 deacetylates and inactivates p53. Regulation of SIRT1 translation

Figure 1. SIRT1: (A) structure and (B) functions and regulation.

largely depends on the stability of its mRNA, which has a relatively long 3'-untranslated region for targeting RNA binding proteins and microRNAs (miRNAs). Tumor suppressor HUR binds to this 3'-untranslated mRNA region to stabilize SIRT1 mRNA and increase SIRT1 translation.⁵⁴ More than 16 miRNAs have been involved in the regulation of SIRT1 translation.⁵⁵ JNK2 phosphorylates SIRT1 and stabilizes it.⁵⁶ Figure 1 depicts the SIRT1 structure, substrates, and activity regulation at different levels.

SIRT1 and Inflammation

Inflammation can be divided into 2 distinct forms: acute and chronic. Figure 2 depicts the different concepts associated with acute and chronic inflammation. Acute inflammation undergoes phase shifts, wherein sets of proinflammatory genes are silenced by the formation of facultative heterochromatin, but other genes (e.g., anti-inflammatory and

metabolic) remain in a euchromatin state; these two states are regulated by SIRT1. In contrast to acute inflammation, chronic inflammation sustains open euchromatin and expression of proinflammatory genes; other genes apparently exist in a silenced state of heterochromatin. The two forms may differentially influence cancer, and SIRT1 plays a distinct role in each.

SIRT1 activity increases as acute inflammation evolves. The acute inflammatory reaction reflects the interplay of innate and adaptive immunity in response to an intense environmental stimulus, often an infection. Innate immune cells initiate acute inflammation, and an adaptive or feed-forward loop that is anti-inflammatory/noninflammatory terminates it. Innate-immunity monocytes/macrophages, granulocytes, and dendritic cells all express Toll-like receptors (TLR) to sense different pathogen-associated molecular patterns and rapidly ignite an

inflammatory response, which virtually always depends on activation of the NFκB family of transcription mediators.⁵⁷ Acute inflammation progresses through 3 phases: initiation (hyperinflammatory response), adaptation (hypoinflammatory response or immunosuppression), and resolution (Fig. 2).⁵⁸ The TLR signal causes phosphorylation and degradation of the inhibitor kinase α (IKBα) that allows NFκB/p65 to translocate to the nucleus and bind gene promoters of inflammatory mediators and other gene classes.⁵⁹ Acetyltransferase p300 activates NFκB/p65 by acetylating lysine residues and inducing a proinflammatory cytokine storm; p65 K310 acetylation is a marker of p65 activation.^{60,61} This rapid proinflammatory gene transcription is rapidly down-regulated (often within hours), and expression of anti-inflammatory genes such as interleukin (IL)-10 and IL-1RA is activated.^{62,63}

The switching of transcription from the early acute inflammatory to the

Figure 2. Inflammation phenotypes. Acute inflammation modifies the chromatin structure to switch from initiation to adaptation and resolution. Chronic inflammation sustains proinflammatory chromatin.

Figure 3. Gain of SIRT1 functions during acute inflammation. TLR responses increase NAMPT-dependent NAD^+ regeneration and activate SIRT1, which represses inflammation, glycolysis, and apoptosis and increases lipolysis, mitochondrial biogenesis, autophagy, and antioxidants. This sequential process restores homeostasis.

adaptive anti-inflammatory state (Fig. 2) is gene specific and regulated by epigenetic reprogramming that requires SIRT1-dependent deacetylation of histone and

nonhistone proteins.⁵⁸ In supporting this temporal sequence, SIRT1 senses redox shifts to integrate bioenergetics with both metabolism and inflammation.^{4,64}

During this time, TLR-mediated, NAMPT-dependent NAD^+ regeneration occurs concomitantly with SIRT1 stabilization and NAD^+ activation of SIRT1 deacetylase activity as the adaptive phase of acute inflammation evolves.⁴⁰ Figure 3 summarizes the pathways involved in the SIRT1-mediated inflammation adaptation.

Specifically, NAD^+ -activated nuclear SIRT1 first deacetylates nonhistone transcription factors. TLR signaling recruits SIRT1 and NMNAT to selected gene promoters by poorly understood pathways, after which they directly interact with promoter-bound $\text{NF}\kappa\text{B}/\text{p}65$.⁴⁸ Local NMNAT-dependent NAD^+ synthesis activates SIRT1 and rapidly terminates $\text{NF}\kappa\text{B}/\text{p}65$ transcription by deacetylating both $\text{p}300$ acetylase on K1020 and K1024 and $\text{NF}\kappa\text{B}/\text{p}65$ on K310.^{61,65}

SIRT1 also deacetylates histone proteins H1K26, H4K16, H3K9, and H3K14 and recruits methyltransferases (G9a and SUV39H1), histone linker H1, heterochromatin protein 1 (HP-1), and DNA CpG methyltransferases DNMT 3a/3b to catalyze DNA methylation, condensing euchromatin to facultative (reversible) heterochromatin.⁶⁶⁻⁶⁸ Simultaneously, SIRT1 promotes the expression of $\text{NF}\kappa\text{B}$ RelB and supports its binding to proinflammatory gene promoters; RelB promoter binding is essential for forming the stable complex that represses the transcription of proinflammatory genes like $\text{TNF-}\alpha$.^{47,69} As acute inflammation resolution proceeds, SIRT1 and RelB dissociate from promoter DNA, and the repressor complex disassembles.

SIRT1's ability to negatively regulate $\text{NF}\kappa\text{B}$ transcription is observed in animal models. In mouse macrophages, knockin of wild-type SIRT1, but not a catalytically inactive SIRT1-H355A mutant, decreases $\text{NF}\kappa\text{B}$ activity and limits acute inflammation. Conversely, knockout of myeloid cell-specific SIRT1 results in the hyperacetylation of $\text{NF}\kappa\text{B}/\text{p}65$, enabling the transcription of

proinflammatory genes, and results in a hyperinflammatory state.^{70,71}

SIRT1 also directs gene reprogramming by modulating inflammatory feedback regulators. I κ B α negatively regulates NF κ B-dependent inflammatory responses by sequestering NF κ B/p65 in the cytoplasm. TLR4 activation quickly degrades I κ B α and activates NF κ B/p65 transcription. In collaboration with RelB, SIRT1 positively regulates I κ B α gene expression and resequesters NF κ B/p65 back to the cytoplasm to attenuate a cytokine storm.⁶⁹

A forkhead family member, FOXO1, enhances NF κ B-mediated inflammation by activating TLR4 upstream signal proteins. Acetylation of FOXO1 by p300 up-regulates TLR4 signaling pathway genes, augmenting the transcription of proinflammatory genes iNOS, TNF- α , and IL-6 in LPS-stimulated macrophages. Ectopic expression of constitutively active FOXO1 in RAW264.7 cells enables LPS-induced phosphorylation of NF κ B/p65 and JNK1/2 and increases LPS-induced gene expression of iNOS and TNF- α . Depletion of FOXO1 expression with a gene-specific shRNA inhibits this effect, and SIRT1 deacetylation of FOXO transcription factors reverses it.⁷²⁻⁷⁴

HIF-1 α promotes the transcription of a series of genes that regulate glycolysis. Importantly, the HIF-1 α -dependent enhanced glycolysis associated with the acute inflammatory process is a Warburg-like response with reduced levels of glucose oxidation by mitochondria. Its NF κ B-dependent expression and stabilization are induced when TLR4 activates macrophages by LPS or by stimulation with TNF- α . HIF-1 α then supports the expression of TLR-mediated proinflammatory genes TNF- α , IL-1, and IL-12, since knocking down HIF-1 α mRNA in macrophages impairs LPS-stimulated proinflammatory gene expression.^{75,76} HIF-1 α -activated transcription requires acetylation at Lys674 by p300. SIRT1 directly interacts with HIF-1 α to deacetylate HIF-1 α at K674, blocking the association of p300 with

HIF-1 α to prevent its activation.⁷⁷ SIRT1 also reduces HIF-1 α -dependent generation of reactive oxygen species (ROS) by repressing UPC expression.^{78,79} Further evidence for this pathway is that resveratrol, an activator of SIRT1 and AMP kinase, inhibits HIF-1 α acetylation and reduces its target gene expression.⁷⁷

Another important mechanism by which SIRT1 negatively regulates inflammation is by supporting autophagy. Autophagy is a collective term for pathways that degrade lysosomes to recycle soluble macromolecules and damaged organelles and plays a well-documented role in the negative regulation of acute inflammation.⁸⁰ Deleting autophagy-related (Atg) genes in macrophages enhances IL-1 β and IL-18 expression in response to LPS.⁸¹ On the one hand, TLR activation of macrophages by LPS causes proinflammatory-mediated damage and defective mitochondrial electron transport chain reactions that produce large amounts of ROS⁸²; hence, activating autophagy to clean the damaged organelles is particularly important for maintaining healthy mitochondria because it removes their dysfunctional parts, generates new parts, and reduces ROS production.^{82,83} On the other hand, TLR activation stimulates Atg/LC3 gene expression. Autophagy activation is determined by SIRT1-mediated deacetylation of Atgs and is NAD⁺ dependent.^{84,85} Increasing NAD⁺ by NAM or SIRT1 activation by resveratrol increases autophagy in peripheral blood mononuclear cells stimulated by LPS. SIRT1 knockout results in the prostatic intraepithelial neoplasia associated with reduced autophagy in mice.⁸⁶

Finally, SIRT1 not only regulated acute inflammation by modifying chromatin and extranuclear proteins, but it also integrates metabolism with the acute inflammatory process by supporting a metabolic switch during adaptation.^{4,5,87} In the initiation phase, TLR activation rapidly increases glucose flux to meet the energy requirement for supporting the expression of proinflammatory genes, increasing antimicrobial activity and

mounting inflammation rapidly. This high-energy reaction activates NADPH oxidase, increases ROS production, and stimulates the expression of HIF-1 α , which switches mitochondrial glucose oxidation to glycolysis; this glycolysis increase is a Warburg-like response with reduced glucose oxidation by mitochondria. As acute inflammation progresses to the adaptation phase, SIRT1 sensing of NAD⁺ directly activates PGC-1 master mediators of mitochondrial biogenesis. This process concomitantly increases the flux of fatty acids by the CD36 membrane transporter and transfer of fatty acids into mitochondria by rate limiting carnitine palmitoyltransferase 1 (CPT-1), providing fat as an alternative source for mitochondrial respiration and other mitochondrial-based events. This metabolic switch from limited glucose oxidation to increased fatty acid oxidation as a source for respiration is NAD⁺, SIRT1, and RelB dependent, since inhibition of NAD⁺ regeneration by NAMPT inhibitor FK866 or RelB knockdown attenuates the increase in fatty acid oxidation and enhances the proinflammatory phase of adaptation. This connection of SIRT1 with Warburg-like glycolysis and a shift to fatty acid oxidation implicates SIRT1 in cancer, as discussed subsequently.

In summary, SIRT1 is a master proximal bioenergy sensor and regulator of the epigenetic processes required to move from the early initiating phase of acute inflammation generated by the rapid expression of proinflammatory mediators to the later adaptation anti-inflammatory phase that may progress to homeostasis. In this process, SIRT1 deactivates NF κ B/p65 and supports expression of the NF κ B family member RelB, which directs euchromatin to silent, but reversible, facultative heterochromatin. Surprisingly, this SIRT1-dependent epigenetic regulation of acute inflammation is coupled to changes in mitochondrial biogenesis and mitochondrial bioenergetics, during which time metabolic paths for using glucose or fatty acids as mitochondrial fuel are switched. The observation that SIRT1

Figure 4. Loss of SIRT1 functions during chronic inflammation. High fat diet reduces NAD⁺ availability and deactivates SIRT1, which promotes inflammation, lipogenesis, insulin resistance, and DNA damage. This unadaptive process prevents a return to homeostasis.

supports the expression of mitochondrial SIRT3 enhances the command position of SIRT1 in inflammation, metabolism, and bioenergetics.

SIRT1 activity diminishes during chronic inflammation. In contrast to acute inflammation, chronic inflammation results from persistent low-level stimulation (Fig. 2). The process lasts a long time, even a life span, and can cause strokes, heart disease, and cancer. In chronic inflammation, there is no apparent adaptation, as is seen in acute inflammation, leading to constant NFκB activation and a mixture of proinflammatory and anti-inflammatory mediators.^{64,88,89} As shown in Figure 4, partial or complete loss of SIRT1 activity is observed in many chronic inflammatory diseases, which might explain the steady hyperactivation of NFκB/p65 in such chronic inflammatory responses as chronic obstructive pulmonary disease (COPD),⁹⁰ obesity,^{91,92} atherosclerosis,⁹³ diabetes,⁹⁴ and aging.⁹⁵ In support of this concept, smokers and COPD patients have

decreased SIRT1 levels in lung alveolar macrophages, airway epithelia, and alveolar epithelia. Moreover, cigarette smoke extract reduces SIRT1 levels in a human monocyte/macrophage cell line (Mono Mac6), leading to hyperacetylation of NFκB/p65 and elevation of IL-8. SIRT1 overexpression in human MonoMac6 cells attenuates the effect.⁹⁶ The mechanisms by which SIRT1 levels diminish during chronic inflammation are poorly understood but involve reduced transcription, increased mRNA degradation, blocked translation, or protein degradation.

Obesity is a rapidly increasing chronic inflammatory disease that increases the risk for a number of adverse health conditions, including hypertension,⁹⁷ high lipid concentration,⁹⁸ type II diabetes,⁹⁹ and cancer.¹⁰⁰ SIRT1 plays a vital role in preventing excessive lipid storage as obesity develops by inhibiting lipogenesis factor PPARγ and increasing the insulin sensitizer adiponectin.¹⁰¹ Mice with adipose

tissue-specific SIRT1 knockout significantly reduce adiponectin but increase leptin levels and adiposity; gene profiles of those on low fat diets overlap to a high degree with wild-type mice on a high fat diet. Both groups have high levels of inflammation-related mediators but low levels of certain mediators that relate to metabolism, especially fat metabolism.^{94,102} There is a close association of SIRT1 levels with body mass index and macrophage recruitment to adipose tissue. Macrophages of the M1 proinflammatory type that are recruited into adipose tissue during obesity have reduced expression of SIRT1.⁹⁴ Also, normal mice treated with SIRT1 antisense oligonucleotides or by fat-specific SIRT1 knockout show significant macrophage infiltration, nuclear NFκB/p65 accumulation, and H3K9 hyperacetylation in white adipose tissue.⁹⁴ Consistent with these changes, several proinflammatory and anti-inflammatory cytokines, including IL-1β, TNF-α, IL-13, IL-10, and IL-4 in plasma, are increased.

Like obesity, aging is associated with chronic diseases and cancers. Increasing evidence supports SIRT1's contribution to slowing the aging process, possibly by 1) silencing gene transcription and activating telomerase activity¹⁰³; 2) repressing UCP expression to decrease ROS production, thereby reprogramming mitochondrial respiration to favor ATP generation by electron chain reaction⁷⁸; and 3) repressing p53-, FOXO1-, and FOXO3-induced apoptosis.¹⁰⁴ Transgenic mice with cardiac-specific overexpression of SIRT1 have delayed aging and protection against oxidative stress in the heart. Mice with somatic SIRT1 knockin achieve a phenotype similar to calorie restriction with a prolonged life span.¹⁰⁵ Conversely, if SIRT1 balance is reduced, aging processes and attendant chronic inflammation are increased.¹⁰⁶ While intriguing, this area of SIRT1 biology and age-associated chronic inflammation is controversial.

Mitochondrial dysfunction is common in diseases associated with chronic

inflammation. Obesity and aging decrease mitochondrial mass and inhibit mitochondrial gene expression but increase glycolysis and the expression of genes supporting glycolysis; reduced mitochondrial oxidation raises the glycolysis energy rate.^{107,108} As mentioned above, HIF-1 α -targeted genes, especially increased pyruvate dehydrogenase lipoamide kinase isozyme 1, reduce glucose mitochondrial oxidation and increase glycolysis during chronic inflammation. This may 1) favor NF κ B/p65 activation to sustain proinflammatory responses, 2) increase intracellular lipid deposition, 3) generate the metabolic syndrome and diabetes, and 4) imbalance mitochondrial physiology. Reduced SIRT1 expression and/or activation could underlie most of these abnormalities of overnutrition,^{109,110} and the association of mitochondrial dysfunction with chronic inflammatory diseases implicates the involvement of other sirtuins. For instance, SIRT3 (controlled by SIRT1), SIRT4, and SIRT5 are mitochondrial proteins, and SIRT3 directly promotes the tricarboxylic acid cycle, oxidative phosphorylation, and many other mitochondrial processes that depend on acetylation and deacetylation.¹¹¹⁻¹¹³ Reductions of SIRT3 are common in cell and animal models of the metabolic syndrome.¹¹⁴ Overexpression of SIRT3 in breast cancer cells with the Warburg metabolic phenotype can switch glycolysis to glucose oxidation, decrease ROS production, and destabilize HIF-1 α .¹¹⁵ Yet, whether the mitochondrial dysfunction is the cause or the outcome of chronic inflammation remains unclear. In contrast, mitochondrial dysfunction clearly plays a role in early acute inflammation and restores during the resolution.^{64,116}

Partial or complete loss of SIRT1 activity in chronic inflammation may contribute to persistent NF κ B/p65 activation and chronic metabolic syndromes; whether insufficient SIRT1 results from or directly generates chronic inflammation is not clear. A persistent low-intensity stimulus like a high fat

diet with SIRT1 degradation and very low dose of LPS prime proinflammation bypass the NF κ B path, which is required for SIRT1 expression and stabilization in acute inflammation, suggesting that insufficient SIRT1 underlies uncontrolled chronic inflammation.¹¹⁷⁻¹¹⁹ What seems clear is that cellular bioenergetics coupled to SIRT1 provides a control axis (positive and negative) that regulates both inflammation, acute or chronic, and cellular and whole organism metabolism.^{40,120}

SIRT1 and Cancer

Connection of chronic inflammation and cancer. Inflammation and its coupling to the innate and adaptive immune response have been associated with carcinogenesis for over a century based on the observations that cancers usually develop in inflammatory tissues, and inflammatory components, such as immune cells, and proinflammatory mediators are present in cancer microenvironments.^{121,122} Epidemiological studies demonstrate that chronic inflammation, dysregulated or recurrent acute inflammation, and infections may contribute up to 20% of all cancers^{13,14}; for example, Crohn disease and ulcerative colitis are associated with increased rates of colon adenocarcinoma,^{123,124} chronic pancreatitis with pancreatic cancer,¹²⁵ chronic bronchitis with lung cancer,¹²⁶ *Helicobacter pylori*-mediated chronic gastritis with gastric cancers,¹²⁷ and acute viral hepatitis B and C infections with hepatocellular carcinoma.¹²⁸ The connection is also supported by the fact that anti-inflammatory therapies may reduce but immunosuppressive drugs may increase the risk for various cancers.¹²⁹⁻¹³¹

Inflammation and cancer are both characterized by such proinflammatory responses as NF κ B-dependent cytokines, chemokines, ROS, and miRNAs. NF κ B activation plays the leading role in these inflammation-induced, cancer-favorable changes. For example, constitutive activation of NF κ B/p65 through paracrine TNF- α stimulation against the

background of chronic hepatitis in Mdr2 knockout mice spontaneously triggered hepatocellular carcinoma, while anti-TNF- α treatment promoted the apoptosis of transformed hepatocytes and the failure to form hepatocellular carcinomas.¹³² The I κ B kinases (IKK) are the upstream activator of NF κ B. Knocking down IKK ϵ using gene-specific shRNA inhibits NF κ B activity, decreases the proliferation of breast cancer cell lines, and inhibits over 70% of breast tumor formation in immunocompromised mice.¹³³

As by-products of the inflammatory response, ROS are an important link in inflammation-induced cancers.¹³⁴ They are small, highly reactive molecules whose production is precisely regulated by superoxide dismutases (SODs), catalases, and peroxidases.¹³⁵ An appropriate amount of ROS activates signaling proteins and helps cells to adapt in response to pathophysiological stimulation, but an excess is cytotoxic, leading to protein and DNA damage, genomic instability, and oncogene expression. Animal studies have demonstrated that ROS are downstream effectors of oncogenes Ras and c-Myc.^{136,137} Heterozygous SOD2^{+/-} mice in which SOD levels are reduced by 50% have a 100% greater tumor incidence than wild-type mice. Inhibiting ROS reverses the oxidative damage.¹³⁸

Inflammatory signals also stimulate the production of noncoding miRNAs in a NF κ B-dependent manner.¹³⁹ These miRNAs are known to participate in the positive or negative regulation of inflammatory response and contribute to carcinogenesis by modulating protein translation. TLR4 activator LPS stimulates the expression of a panel of miRNAs, such as miR-146a, miR-132, miR-155, miR-25, and miR-32 in a human acute monocytic leukemia cell line (THP-1 cells).¹⁴⁰ miR-146a negatively feedback regulates TLR4 signaling and reduces TNF- α transcription and translation by inhibiting downstream IL-1 receptor-associated kinase and TNF receptor-associated factor 6¹⁴¹;

Figure 5. Dual effects of SIRT1 on cancer: (A) inflammation and (B) modifying specific proteins.

miR-155 has been reported to down-regulate transcriptional suppressors and promote cell proliferation in *in vitro* cell culture and *in vivo* animal models. Elevated hematopoietic miR-155 promotes lymphoma¹⁴²⁻¹⁴⁴; miR-25 and miR-32 stimulate p53 expression by directly targeting negative regulators of p53 and the mTOR (mammalian target of rapamycin) pathway, respectively, which inhibits cellular proliferation. Overexpression of miR-25 and miR-32 inhibits the growth of glioblastoma multiforme cells in the mouse brain.¹⁴⁵

With the major contributions of inflammation to cancer and the major but distinct contributions of SIRT1 to inflammation, it stands to reason that SIRT1 will have multiple effects on cancer (Fig. 5).

Dual functions of SIRT1 during carcinogenesis. Cancer has 7 hallmarks: the self-sufficiency of growth signals, insensitivity to antigrowth signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, tissue invasion

and metastasis, and inflammation.^{146,147} Inflammation shares all of these except metastasis and limitless replicative potential (transformation). As discussed previously, SIRT1 directly interacts with p53 and HIC1, counters the Warburg glycolysis, favors catabolism with increased fatty acid oxidation, and modifies ROS by mitochondria. Moreover, the SIRT1 partner of inflammation, RelB, is classified as an oncogene.¹⁴⁸ Strong evidence implicates SIRT1 as a tumor promoter.

First, evidence that SIRT1 acts as a tumor promoter stems from the discovery of p53 as its first nonhistone substrate. SIRT1 physically interacts with p53 and deacetylates p53 K382, inhibiting p53 from transactivating apoptotic genes and promoting apoptosis of injured cells but favoring cell growth.⁴⁴ These observations support that SIRT1 is an oncogene. In further support, SIRT1 is significantly elevated in human prostate cancer,¹⁴⁹ leukemia,¹⁵⁰ primary colon cancer,¹⁵¹ and all nonmelanoma skin cancers among others.¹⁵² Its overexpression in cancer cells aligns with the

dysregulation by tumor suppressor genes. For example, epigenetic silencing of HIC1 during aging interrupts the HIC1-SIRT-p53 loop to elevate SIRT1 levels.⁵² High levels of SIRT1 contribute to cancer cell growth mostly through the deacetylation of tumor suppressor gene p53 to repress p53 apoptotic activity. Overexpression of SIRT1 but not its catalytic mutant hampers p53-dependent cell cycle arrest and apoptosis in response to DNA damage and oxidative stress. Inhibiting SIRT1 activity causes p53 hyperacetylation and, as a consequence, increases p53-dependent apoptotic gene transcription.^{153,154}

Second, SIRT1's oncogenic effect also may be attributed to loss of function of the SIRT1 inhibitor DBC1. DBC1 physically interacts with SIRT1 to negatively regulate its activity, leading to p53 hyperacetylation and p53-mediated apoptosis. Deleting DBC1 in breast cell lines reverses SIRT1 inhibition and increases the risk for cancer.^{34,43}

Third, overexpressed SIRT1 represses other tumor suppressor genes through epigenetic modulation of transcription activators or repressors. Typical SIRT1 substrates are the FOXO family, E2F1, Rb, BCL6, and Ku70, which are all important for DNA damage repair.¹⁵⁵ SIRT1 also epigenetically modulates histone substrates to regulate cancer-related gene expression and stabilize genomic DNA. Loss of global H4K16ac and H4K20me3 is a hallmark of human tumors.¹⁵⁶ SIRT1 deacetylates H4K16 and H3K9 at promoters of several tumor suppressor genes, stabilizing and recruiting methyltransferases SUV39H1 to them to prompt histone hypermethylation. At the same time, SIRT1 stimulates heterochromatin formation and silences tumor suppressor genes.¹⁵⁷⁻¹⁶⁰

However, studies supporting SIRT1 as a cancer promoter in animal models are controversial. A transgenic strain of p53^{+/-} mice that overexpressed SIRT1 had less thymic lymphoma and better survival following exposure to γ -irradiation.¹⁶¹ Yet, in another study, SIRT1 overexpression in mice prevents

the metabolic syndrome and can improve obesity but does not increase tumor formation.^{162,163} Instead, elevated SIRT1 protein or activation enhanced chemoresistance to various cancers.^{164,165}

Further evidence for SIRT1 as an oncogene is that it supports the survival of cancer stem cells (CSCs). This old idea of stem cells in cancer recently has attracted special attention from oncologists. According to this theory, CSCs, like normal stem cells, can self-renew for generations and give rise to the various differentiated cells found in the malignancy. Some hypothesize that CSCs cause relapses after anticancer therapies.¹⁶⁶ SIRT1 overexpression sustains CSC activities in different cancers. In chronic myelogenous leukemia (CML), for example, SIRT1 is overexpressed in CD34⁺ stem cells and contributes to CD34⁺ cell survival by repressing p53-mediated apoptosis of CML CSCs. Hence, overexpressed SIRT1 can explain CML resistance to chemotherapy with tyrosine kinase inhibitors. Inhibiting SIRT1 in CML CD34⁺ stem cells either by shRNA or the small molecular inhibitor tenovin-6 represses CD34⁺ colony growth and impairs CML CSC engraftment.¹⁶⁷

Despite the oncogenic role of SIRT1 via p53 and other partners, SIRT1 is often decreased in chronic inflammation that is a risk for cancer (e.g., obesity). In support of this, down-regulated SIRT1 expression occurs in glioblastoma, bladder carcinoma, prostate carcinoma, ovarian cancer, and hepatic carcinoma.¹⁵⁷ Its deficiency also hampers DNA repair and causes severe genetic instability. Normal BRCA1 is a tumor suppressor and a positive regulator of SIRT1 gene transcription. Its mutation reduces SIRT1 expression and increases the risk for breast, ovarian, fallopian tube, and prostate cancer.¹⁶⁸ Using resveratrol to restore or activate SIRT1 in BRCA1 mutant cancer cells compensated for the loss of function, stimulated apoptosis, and inhibited tumor formation in both *in vitro* cell culture and *in vivo* animal models.¹⁶⁹

Further evidence that low levels of SIRT1 may promote cancer growth is the research on survivin, a tumor promoter expressed in most cancer cell types but not normal cells.¹⁷⁰⁻¹⁷² SIRT1 represses survivin gene transcription by deacetylating H3K9 at its promoter.¹⁶⁹ SIRT1 expression in BRCA1 mutant cancer cells reduces survivin expression and inhibits tumor formation. β -catenin is another tumor promoter gene with constitutive contributions in breast, ovarian, and colorectal cancers and melanoma.¹⁷³⁻¹⁷⁶ SIRT1 deacetylates this protein and represses its nuclear translocation and transactivation activity. SIRT1 overexpression in *APC*^{min/+} mice localizes oncogenic β -catenin in the cytoplasm and consequently inhibits the development of colon cancer.¹⁷⁴

We have not discussed the relationships among SIRT1, autophagy, and cancer in this review. Autophagy as a broad concept plays a complex role in inflammation that may be good for chronic inflammation and bad during the early acute inflammatory induction of mitophagy. It is not surprising that there may be good sides and bad sides of the SIRT1 link to autophagy in cancer.^{177,178}

Perspective

SIRT1's role as a bioenergy sensor, chromatin, and protein modifier lies along with its family—at the foundation of cell biology. It is not surprising that this pivotal molecule influences both health and disease. But what are the nuances? Healthy acute inflammation apparently uses the SIRT1 axis in concert with NF κ B and autophagy pathways as a nexus of the orderly and sequential epigenetic and signaling shifts necessary to balance and integrate the inflammatory process with metabolic demands for defense and healing. However, sustained, intense SIRT1 activity as seen in the second phase of acute inflammation is harmful, at least sustained immunosuppression, a concept with implications for SIRT1 inhibitors.¹⁷⁹ In chronic inflammation, low SIRT1 activity may allow a steady trickle of

inflammation without adaptation, a concept with major implications for SIRT1 activators. There is a similar state in cancer. Increased SIRT1 can clearly promote some cancers by directly disrupting tumor repressors like p53, while low levels of SIRT1 may promote cancer by increasing DNA damage and limited DNA repair, confounding SIRT1 therapeutic approaches in cancer.

Therefore, balance, or yin/yang, is the take-home message about SIRT1. The following questions might improve the understanding of this remarkable chameleon-like molecule.

1. How does SIRT1 bioenergy sensing differ by cell- or tissue-type specificity in acute and chronic inflammation?
2. Does SIRT1 regulate myeloid-derived suppressor cells associated with inflammation or cancer in bone marrow or local sites?
3. What is the interplay of SIRT1 in regulating the exome and transcriptome chromatin landscape of specific inflammatory or cancer processes?
4. How can we identify phenotypes that might benefit from SIRT1-based therapeutics?
5. How does SIRT1 mitochondrial regulation impact inflammation and cancer?
6. What is the collective dance of the sirtuin family in inflammation and cancer?

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