SIRT1-NF-κB Axis

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Inflammation is an adaptive response triggered by harmful conditions or stimuli, such as an infection or tissue damage pursuing homeostasis reestablishment. Liver diseases cause approximately 2 million deaths per year worldwide and hepatic inflammation is a common factor to all of them, being the main driver of hepatic tissue damage and causing progression from NAFLD (non-alcoholic fatty liver disease) to NASH (non-alcoholic steatohepatitis), cirrhosis and, ultimately, HCC (hepatocellular carcinoma). The metabolic sensor SIRT1, a class III histone deacetylase with strong expression in metabolic tissues such as liver, and transcription factor NF-κB, a master regulator of inflammatory response, show an antagonistic relationship in controlling inflammation. For this reason, SIRT1 targeting is emerging as a potential strategy to improve different metabolic and/or inflammatory pathologies. In this review, we explore diverse upstream regulators and some natural/synthetic activators of SIRT1 as possible therapeutic treatment for liver diseases.

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1. SIRT1 in Liver Metabolism

In the liver, SIRT1 partially regulates glucose, lipids and cholesterol metabolism. Of note, changes in the concentration of nutrients and hormones during fasting/intake periods control the expression of SIRT1 [1].

During fasting, there is an initial increase in glucagon levels, produced by pancreatic alpha cells, which leads to a rise in gene transcription of both SIRT1 and gluconeogenesis genes in the liver, through the cyclic AMP response element-binding protein (CREB) and its co-activator protein, CREB-regulated transcription coactivator 2 (CRTC2) [1][2]. Gluconeogenesis is an anabolic pathway of metabolism that allows glucose biosynthesis from different sources: glucogenic amino acids, lactate, glycerol or tricarboxylic acid (TCA) cycle intermediates [3]. If fasting is prolonged, SIRT1 first deacetylates CRTC2 protein, which results in its targeting for ubiquitinization and degradation by the proteasome. Secondly, SIRT1 deacetylates peroxisome proliferator-activated receptor γ coactivator 1-α (PGC1-α) and forkhead box O1 (FOXO1), key participants in β-oxidation and gluconeogenesis regulation, increasing their transcriptional activity [4]. On the one hand, deacetylation and activation of PGC1-α by SIRT1 results in increased fatty acid oxidation and improved glucose homeostasis [5]. On the other hand, the activation of FOXO1, by its deacetylation by SIRT1, increases gluconeogenesis [6]. In this way, the maintenance of both metabolic processes can supply the body's energy needs during prolonged fasting. In contrast, under nutrient intake conditions, carbohydrate-responsive element-binding protein (ChREBP) transcription factor, induced by circulating high glucose and fatty acids levels, represses the expression of SIRT1 [7].

SIRT1 not only regulates glucose metabolism in the liver, but also lipids and cholesterol homeostasis. During fasting, free fatty acids are released from adipose tissue and subjected to β-oxidation in the liver to provide energy [3]. By contrast, under fed conditions, liver synthesizes fatty acids (lipogenesis), which are then stored in adipose tissue [3]. In a starving state, SIRT1 promotes fatty acid oxidation by activating peroxisome proliferator-activated receptor α (PPAR-α) [2]. PPAR-α is a transcription factor able to bind fatty acids, and whose union unleashes an increase in expression of genes related to fatty acid catabolism in the mitochondrial matrix [2]. SIRT1 enhances PPAR-α activation by deacetylating the co-activator of PPAR-α: PGC1-α [2]. Additionally, SIRT1 deacetylates sterol regulatory element-binding protein 1 (SREBP1) transcription factor, targeting it for degradation via ubiquitin/proteasome system, which results in hepatic repression of lipids and cholesterol synthesis [8]. SIRT1 also facilitates the action of oxysterols liver X receptor α (LXR-α), whose target gene, ATP-binding cassette transporter A1 (ABCA1), is responsible for high-density lipoprotein (HDL) particle synthesis and reverse cholesterol transport, from peripheral tissues to liver, where it can be secreted into bile [9]. Finally, SIRT1 also regulates cholesterol homeostasis via farnesoid X receptor (FXR), important for bile acids biosynthesis and cholesterol catabolic pathways. Deacetylation of FXR by SIRT1 produces, on the one hand, receptor activation, increasing bile acid synthesis and, on the other hand, it has a positive feedback effect over SIRT1 transcription [10].

2. SIRT1 in NF-κB Mediated Inflammation

Inflammation is an adaptive response aimed at restoring homeostasis altered by harmful stimuli, such as infection or tissue damage [11]. During the inflammatory response, several phases develop, starting with an initial pro-inflammatory phase, passing through the adaptive phase and ending with the reinstatement of homeostasis [11]. The switch between the pro-inflammatory and adaptive phase requires a metabolic change from an anabolic state to a catabolic state that depends on the sensing of adenosine monophosphate (AMP) and NAD^+ levels by AMP-activated protein kinase (AMPK) and sirtuins, respectively. In this way, AMPK and sirtuins are able to couple inflammation and metabolism with chromatin state and gene transcription [12].

The nuclear factor kappa B (NF-κB) is a family of inducible transcription factors present in numerous cell types and integrated by seven different members, which form homo and heterodimers: NF-κB1 (p105 and p50), NF-κB2 (p100 and p52), RelA (p65), RelB and c-Rel [13]. NF-κB is considered as a major regulator of the inflammatory response due to its ability to regulate the transcription of genes involved in the establishment of immune and inflammatory response [13][14]. Its regulation occurs at several levels and, to date, three ways have been identified for NF-κB activation: (1) the canonical one, triggered mainly by cytokines such as TNF-α or IL1, and by toll-like receptor (TLR) agonists; (2) the non-canonical one, with an important function in B lymphocytes and (3) the activation induced by DNA damage [15][16]. A second level of regulation is post-translational modifications of NF-κB subunits, carried out by various proteins, including the IκB kinase (IKK) complex. Some of these modifications include processes of phosphorylation, acetylation, ubiquitination and prolyl isomerization, which regulates NF-κB activity by modulating its nuclear translocation, DNA binding, transactivation and interaction with CBP/p300-interacting transactivator 1 [17].

In quiescent cells, NF-κB is located in the cytoplasm, associated with inhibitory proteins (IκB-α, IκB-β, IκB-γ, IκBNS, Bcl-3) and some precursor proteins such as p100 and p105 (which, once cleaved, give rise to p52 and p50 subunits, respectively) [16]. In the canonical activation pathway, upon arrival of a stimulus to the cell, a phosphorylation occurs, followed by ubiquitination and degradation of its inhibitory proteins, in a proteasome dependent-manner. This releases NF-κB, which is then translocated to the nucleus, where it functions by activating gene transcription [18].

Both, NF-κB and SIRT1 signaling pathways are evolutionarily conserved mechanisms for the maintenance of homeostasis and whose interaction allows energy balance to be coupled with the immune/inflammatory response [19]. However, the nature of this relationship is antagonistic, so that SIRT1 is capable of inhibiting NF-κB signaling, and vice versa. This antagonism is explained based on two reasons. On the one hand, the body needs to adapt the metabolism to a rapid energy generation system that allows it to respond quickly to a harmful stimulus (such as an infection or tissue damage). On the other hand, it is necessary to re-establish homeostasis conditions once the harmful stimulus has disappeared [19]. Failure to resolve the inflammation would lead to a chronic inflammatory condition, typical of chronic liver diseases [20].

A direct association between SIRT1 and RelA/p65 subunit of NF-κB has been described: SIRT1 is able to deacetylate lysine 310 of RelA/p65 subunit, affecting its transcriptional activity and decreasing expression of its anti-apoptotic and pro-inflammatory target genes [21]. Additionally, deacetylation of RelA/p65 at lysine 310 facilitates methylation at lysines 314 and 315, which is important for the ubiquitination and degradation of RelA/p65 [22][23]. The different acetylations/ deacetylations of RelA/p65 can have various effects on NF-κB regulation but, particularly, deacetylation of RelA/p65 by SIRT1 favors the association of p65/p50 complex (the most abundant heterodimer of NF-κB [15][22][23]) with IκB-α (an inhibitor of NF-κB). This association triggers the transport of the NF-κB complex from the nucleus back to the cytoplasm and, therefore, inactivates the activity of NF-κB . Furthermore, several authors have observed the possibility of forming complexes between PGC1-α/PPARs and NF-κB, enhanced by SIRT1, triggering repressive effects on the development of the inflammatory response (reviewed by Kauppinen et al. [19]).

Interestingly, a possible regulatory action of NF-κB on SIRT1 has also been suggested, since regions flanking the SIRT1 gene, both in mice and humans, contain numerous NF-κB binding elements [24][25]. In fact, some authors have already described this possible interaction. For example, Yamakuchi et al. [26] showed that the microRNA 34a (miR-34a) inhibits the expression of SIRT1 by binding to its 3′ UTR region; and Li et al. [27] described the mechanism by which NF-κB, through binding to the promoter region of miR-34a, is able to increase its level of expression. It should be noted that another miR-34a-controlled gene is AXL, a tyrosine kinase receptor that our group has implicated in the development of liver fibrosis [28], particularly in experimental NASH models and patients [29]. A link between AXL expression and SIRT1 has recently been reported in tissue macrophages [30] and may provide new targets for clinical treatment. Whether SIRT1/AXL can act in a coordinated manner and play a role in the progression of chronic liver disease is an aspect that deserves further studies.

Moreover, some factors, as oxidative stress or interferon γ (IFN-γ), can also suppress SIRT1 transcription or activity [27][31][32]. At the same time, NF-κB could induce oxidative stress through the enhancement of expression of ROS generating enzymes, such as NADPH oxidase (NOX) [33][34]. Additionally, it seems that NF-κB could interact with IFN-γ promoter [35]. Similarly, another study demonstrated that another microRNA, miR-378, is a key player in modulating NASH via TNF-α signaling. In particular, miR-378 acts as an important component of the molecular circuit composed by miR-378, AMPK, SIRT1, NF-κB and TNF-α to induce spontaneous activation of inflammatory genes with potential implications in NASH pathogenesis [36].

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