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Review

Antagonistic crosstalk between NF-κB and SIRT1 in the regulation of inflammation and metabolic disorders

Anu Kauppinen [a], Tiina Suuronen [b], Johanna Ojala [b], Kai Kaarniranta [a,c], Antero Salminen [b,d,*]

[a] Department of Ophthalmology, Institute of Clinical Medicine, University of Eastern Finland, P.O. Box 1627, FIN-70211 Kuopio, Finland
[b] Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland, P.O. Box 1627, FIN-70211 Kuopio, Finland
[c] Department of Ophthalmology, Kuopio University Hospital, P.O. Box 1777, FIN-70211 Kuopio, Finland
[d] Department of Neurology, Kuopio University Hospital, P.O. Box 1777, FIN-70211 Kuopio, Finland

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ABSTRACT

Recent studies have indicated that the regulation of innate immunity and energy metabolism are connected together through an antagonistic crosstalk between NF-κB and SIRT1 signaling pathways. NF-κB signaling has a major role in innate immunity defense while SIRT1 regulates the oxidative respiration and cellular survival. However, NF-κB signaling can stimulate glycolytic energy flux during acute inflammation, whereas SIRT1 activation inhibits NF-κB signaling and enhances oxidative metabolism and the resolution of inflammation. SIRT1 inhibits NF-κB signaling directly by deacetylating the p65 subunit of NF-κB complex. SIRT1 stimulates oxidative energy production via the activation of AMPK, PPARα and PGC-1α and simultaneously, these factors inhibit NF-κB signaling and suppress inflammation. On the other hand, NF-κB signaling down-regulates SIRT1 activity through the expression of miR-34a, IFNγ, and reactive oxygen species. The inhibition of SIRT1 disrupts oxidative energy metabolism and stimulates the NF-κB-induced inflammatory responses present in many chronic metabolic and age-related diseases. We will examine the molecular mechanisms of the antagonistic signaling between NF-κB and SIRT1 and describe how this crosstalk controls inflammatory process and energy metabolism. In addition, we will discuss how disturbances in this signaling crosstalk induce the appearance of chronic inflammation in metabolic diseases.

Contents

Abbreviations: AGRP, agouti-related protein; AMPK, AMP-activated protein kinase; AP-1, activator protein-1; BCL10, B-cell lymphoma/leukemia-10; CIITA, class II, major histocompatibility complex, transactivator; DHA, docosahexaenoic acid; E2F1, transcription factor E2F1; EPA, eicosapentaenoic acid; ERK, extracellular signal-regulated kinase; FoxO, Forkhead box O protein; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; HIC1, hypermethylated in cancer-1; HIF, hypoxia-inducible factor; IκBα, inhibitor of κB protein-α; IAP-2, inhibitor of apoptosis-2; IFN-γ, interferon-γ; IKK, inhibitory-κB kinase; IL, interleukin; JAK, Janus kinase; LKB1, serine/threonine kinase 11; LPS, lipopolysaccharide; M1, classically activated proinflammatory macrophage; M2, alternatively activated anti-inflammatory macrophage; MCP-1, monocyte chemotactic protein-1; miR, microRNAs; NAD, nicotinamide adenine dinucleotide; NAMPT, nicotinamide mononucleotide adenylyltransferase; NF-κB, nuclear factor-κB; NLR, nucleotide-binding domain leucine-rich repeat-containing receptor; NOS, nitric oxide synthase; PARP-1, poly(ADP-ribose) polymerase-1; PDK4, pyruvate dehydrogenase kinase 4; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PHD, prolyl-hydroxylase domain-containing protein; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SF1, steroidogenic factor 1; SIRT1, silent information regulator 1; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor β; TLR, Toll-like receptor; SUMO, small ubiquitin-like modifier; TNFα, tumor necrosis factor-α; UTR, untranslated region.

* Corresponding author at: Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland, P.O. Box 1627, FIN-70211 Kuopio, Finland. Tel.: +358 505740740; fax: +358 17162048.
E-mail address: antero.salminen@uef.fi (A. Salminen).

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1. Introduction

There are emerging studies demonstrating that there is a close molecular coordination between different phases of inflammation and the energy metabolic supply [1–3]. Inflammation is an innate host defense mechanism mounted against infections and a variety of tissue injuries. The inflammatory process involves distinct stages, such as acute, adaptive, and resolution phases, and moreover, inflammation can proceed to a chronic condition, e.g. in autoimmune diseases and many metabolic and age-related degenerative diseases. The NF-κB system has a critical role in regulating the innate immunity responses provoked by immune cells in host tissues [4]. There is abundant evidence indicating that NF-κB signaling can also control energy metabolic shifts in coordination with SIRT1, a major regulator of energy metabolism and tissue survival [5–7].

The NF-κB signaling pathway and SIRT1 enzyme are evolutionarily conserved mechanisms in the maintenance of cellular homeostasis. This means that these signaling pathways interact to integrate energy metabolism to immune responses and it seems that the regulation is disturbed in many chronic diseases, such as obesity, type 2 diabetes, and atherosclerosis [5,8]. Interestingly, NF-κB and SIRT1 demonstrate the characteristics of antagonistic crosstalk, i.e. NF-κB is driving a pro-inflammatory phenotype with glycolytic metabolism, whereas SIRT1 supports oxidative respiration and anti-inflammatory responses, also enhancing the resolution of inflammation (Fig. 1). This antagonism is crucial for the survival of the organism since the ability to respond promptly to aggressive pathogens and tissue damage requires quick switches in energy production. On the other hand, the acute inflammatory condition needs to be resolved when the threat has disappeared, if not, this can lead to detrimental chronic inflammation, as observed in many metabolic diseases. We will examine the mechanisms of antagonistic signaling between NF-κB and SIRT1, and how the innate immunity responses are coordinated with energy metabolism. Moreover, we will briefly discuss how disturbances in this crosstalk can lead to chronic inflammation in metabolic diseases.

2. Antagonistic crosstalk between SIRT1 and NF-κB

SIRT1 and the NF-κB system represent ancient signaling pathways which regulate metabolic and inflammatory networks in mammals through mutually opposing control mechanisms. SIRT1 can inhibit NF-κB signaling directly or indirectly, in turn the NF-κB system suppresses SIRT1-mediated functions by inhibiting the downstream targets of SIRT1. Given that SIRT1 and NF-κB signaling have antagonistic characteristics, these pathways control many of the physiologically relevant metabolic and inflammatory switches required for the maintenance of cellular and organismal homeostasis.

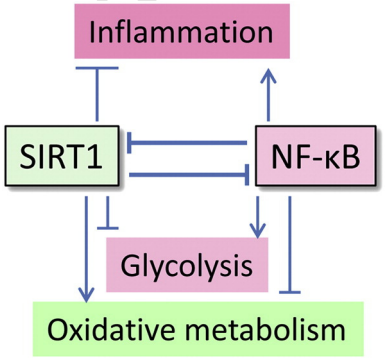

Fig. 1. A schematic presentation on the antagonistic regulation between NF-κB and SIRT1 signaling in the control of inflammation and metabolic responses.

2.1. SIRT1 inhibits NF-κB signaling

In their seminal study in 2004, Yeung et al. [9] demonstrated that SIRT1 could directly interact with and deacetylate the RelA/p65 component of the NF-κB complex. The deacetylation of Lys310 inhibited the transactivation capacity of RelA/p65 subunit and consequently suppressed the transcription of the NF-κB-dependent gene expression. Moreover, deacetylation of Lys310 in the RelA/p65 protein exposed it to methylation at Lys314 and Lys315 which enhanced its ubiquitination and degradation [10]. A plethora of recent studies have confirmed that SIRT1 indeed inhibited the NF-κB signaling, and the activation of SIRT1 could alleviate a multitude of NF-κB-driven inflammatory and metabolic disorders [11–14] (Fig. 2). This implies that SIRT1 activators could exert significant benefits in the treatment of metabolic and inflammatory disorders.

Yeung et al. [9] made another important observation when they reported that SIRT1 was localized to NF-κB sites in the promoter of *cIAP-2* gene. Additionally, resveratrol, an activator of SIRT1, caused the loss of acetylation at H3K14, and consequently suppressed the transcription of the *cIAP-2* gene after TNF-α treatment. Moreover, they revealed that the SIRT1 recruitment to the NF-κB sites in chromatin was a promoter-specific event since SIRT1 was not present in

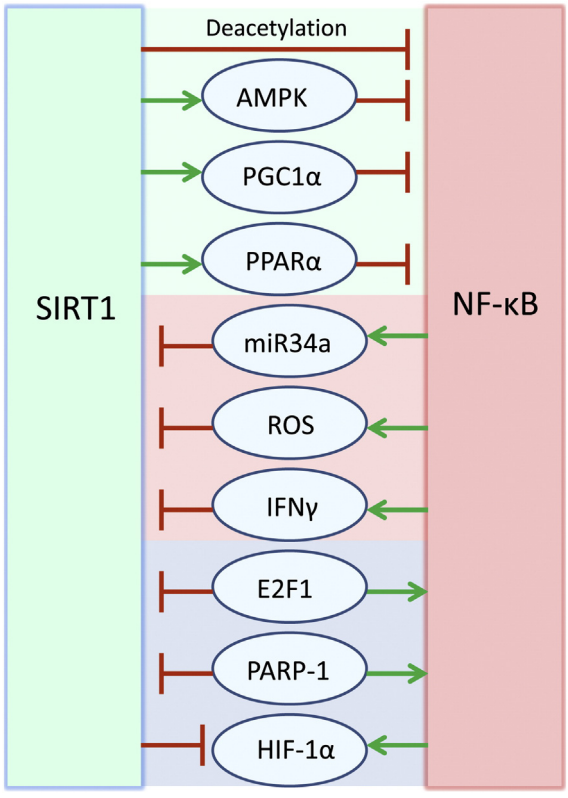

Fig. 2. The major signaling pathways mediating the antagonistic regulation between NF-κB and SIRT1. See Abbreviations.

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