

METABOLIC REPROGRAMMING DRIVEN BY THE NAD⁺/SIRT1-PARP1 AXIS: IMPLICATIONS FOR GENOMIC STABILITY, DNA DAMAGE RESPONSE, AND THERAPEUTIC RESISTANCE IN CANCER

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RESUMO

Introduction: Cancer cells undergo profound metabolic reprogramming to sustain proliferation, survival, and stress adaptation. Among the central regulators of this process, the NAD⁺-dependent signaling network, particularly the interplay between sirtuin 1 (SIRT1) and poly(ADP-ribose) polymerase 1 (PARP1), has emerged as a critical determinant of genomic stability and therapeutic response. **Objective:** This review aims to elucidate the role of the NAD⁺/SIRT1-PARP1 axis in coordinating metabolic adaptation, DNA damage repair, and resistance to anticancer therapies. **Materials and Methods:** This narrative review employed a systematic search strategy in PubMed/MEDLINE and Scopus. Terms such as “NAD⁺ metabolism,” “SIRT1,” “PARP1,” “DNA damage response,” and “cancer metabolism” were combined using Boolean operators. Original articles, systematic reviews, and meta-analyses focusing on molecular and metabolic mechanisms in cancer were included. Data were qualitatively synthesized to highlight the interplay among NAD⁺ signaling, genomic stability, and therapeutic resistance. **Results:** Current evidence indicates that increased PARP1 activity in response to DNA damage leads to substantial NAD⁺ consumption, thereby limiting its availability for SIRT1 activity. This imbalance disrupts key cellular processes, including chromatin remodeling, mitochondrial function, and the regulation of oxidative stress. Conversely, SIRT1 modulates DNA repair pathways, promotes genomic integrity, and regulates transcriptional programs involved in cell survival and metabolism. The competition for NAD⁺ between these enzymes establishes a metabolic checkpoint that influences tumor progression and cellular fate. Furthermore, alterations in NAD⁺ metabolism have been associated with resistance to chemotherapy and radiotherapy, highlighting the therapeutic potential of targeting this axis. Pharmacological modulation of PARP1 and SIRT1, as well as strategies aimed at restoring NAD⁺ homeostasis, may enhance treatment efficacy and overcome resistance mechanisms. **Conclusion:** The NAD⁺/SIRT1-PARP1 axis plays a central role in linking metabolism, genomic stability, and cancer progression. Its dysregulation contributes to therapeutic resistance, while targeting NAD⁺ homeostasis and related pathways represents a promising strategy to improve anticancer treatment outcomes.

Palavras-chave: NAD⁺ Metabolism SIRT1 PARP1 Metabolic Reprogramming DNA Damage Response Cancer.