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Role of Sirtuins in Tumor Angiogenesis

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Generally, changes in the metabolic status of cells under conditions like hypoxia and accumulation of lactate can be sensed by various sensing mechanisms, leading to modulation of a number of signal transduction pathways and transcription factors. Several of the proangiogenic cytokines like VEGF, FGF, PDGF, TGF-β, Ang-2, ILs, etc. are secreted by cancer cells, under hypoxic microenvironment. These cytokines bind to their receptors on the endothelial cells and activates a number of signaling pathways including Akt/PIP3, Src, p38/MAPK, Smad2/3, etc., which ultimately results in the proliferation and migration of endothelial cells. Transcription factors that are activated in response to the metabolic status of tumors include HIFs, NF-κb, p53, EI-2, and FOXO. Many of these transcription factors has been reported to be regulated by a class of histone deacetylase called sirtuins. Sirtuins are NAD^+ dependent histone deacetylases that play pivotal role in the regulation of tumor cell metabolism, proliferation, migration and angiogenesis. The major function of sirtuins include, deacetylation of histones as well as some non-histone proteins like NF-κB, FOXOs, PPARϒ, PGC1-α, enzymes like acetyl coenzymeA and structural proteins like α tubulin. In the cell, sirtuins are generally considered as the redox sensors and their activities are dependent on the metabolic status of the cell. Understanding the intricate regulatory mechanisms adopted by sirtuins, is crucial in devising effective therapeutic strategies against angiogenesis, metastasis and tumor progression. Keeping this in mind, the present review focuses on the role of sirtuins in the process of tumor angiogenesis and the regulatory mechanisms employed by them.

Keywords: sirtuins, tumor angiogenesis, metabolism, histone deacetylases, endothelial cells, signaling pathways

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INTRODUCTION

Angiogenesis, the process of formation of new blood vessels from pre-existing ones, is essential for the normal growth, development and wound healing. Apart from this, angiogenesis is also inevitable for tumor growth and metastasis (1–5). The expression and secretion of various modulators of angiogenesis is regulated by microenvironmental factors like hypoxia and accumulation of different metabolites (6–8). Under conditions like hypoxia, a number of signal transduction pathways and transcription factors like PPARα, PGC-1α, AMPK, FOXOs, etc. gets activated (9, 10). The expression and activation of these transcription factors has been reported to be regulated by a class of histone deacetylase called sirtuins or SIRT (11, 12). Sirtuins are NAD^+ dependent histone deacetylases that play a vital role in the regulation of metabolism, aging, oncogenesis, angiogenesis and cancer progression (13, 14). It has been reported that SIRT1 can function as a redox sensor, and its activity might be dependent on the overall metabolic status of the