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SIRT1: Functionalities of the biological holy grail

Sagnik Roy

This article discusses the importance of a biologically potent molecule named, Sirtuin 1 (SIRT1). It is a nicotinamide adenine dinucleotide (NAD)+ dependent enzyme, a class-III histone deacetylase (HDAC). SIRT1 deacetylation of peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) is a key factor in mitochondrial biogenesis and metabolic control and is important for the turnover of defective mitochondria by mitophagy. It deacetylates both histone and non-histone targets and thus is important in the epigenetic regulation of tissue homeostasis. It is a tumour suppressor and a tumour promoter. Checkpoint kinase 2 (CHK2) mediation of SIRT1 function in cell cycle progression is capable of providing new insights for cellular homeostasis modulation and genomic integrity maintenance to prevent ageing and cancer. SIRT1 upregulation and downregulation play key roles in acute myeloid leukaemia (AML) and primary colorectal cancer, prostate cancer, melanoma, non-melanoma skin cancers, breast cancer, and hepatic cell carcinomas. SIRT1 plays an important role in the pathway of forkhead transcription factors, mechanistic of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and Wnt1 inducible signalling pathway protein 1 (WISP1). SIRT1’s efficient regulation of non-coding RNAs may either extend or end cellular survival. SIRT1 inhibition has shown to prevent leukaemic stem cells and residual disease in the chronic phase of chronic myelogenous leukaemia (CML). SIRT1 is important in alleviating hepatic insults and in the treatment of xenobiotic-induced hepatotoxicity and is a therapeutic target for treating alcoholic and nonalcoholic fatty liver diseases.

SIRT1 promotes axonal elongation, neurite outgrowth, and dendritic branching, and plays key roles in hypothalamic functions, Alzheimer's, Parkinson's, and motor neuron diseases, and memory formation. It is a potential gene target of depression treatment. From an artificial skin development perspective, SIRT1 plays important roles in efficient wound healing, regeneration of both the epidermis and the dermal stroma, production of many cytokines, recruitment of macrophages, neutrophils, and mast cells, the recruitment, and activation of fibroblasts, and angiogenesis in the granulation tissue and epithelial-mesenchymal transition (EMT), cell migration, and transforming growth factor (TGF)-β signalling in keratinocytes. Studies have revealed that overexpression of SIRT1 during macrophage differentiation increases their proliferative capacity, while a decrease of SIRT1 expression restricts macrophage self-renewal in culture. SIRT1 inhibition or deficiency increases endoplasmic reticulum (ER) stress-induced cardiac injury; whereas, activation of SIRT1 prevents cardiac injury. In signalling pathways, SIRT1’s interactions with protein substrates prevent toxic damage caused by toxicants. Researchers believe that SIRT1 has the potential to revert the disease process and possibly extend a healthy human lifespan.

Keywords: SIRT1, Histone deacetylase (HDAC), Peroxisome, Fibroblasts, Keratinocytes, Macrophage

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