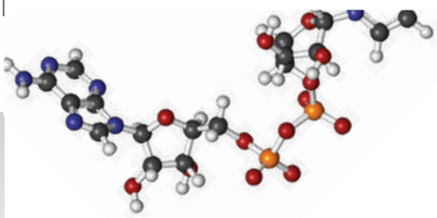

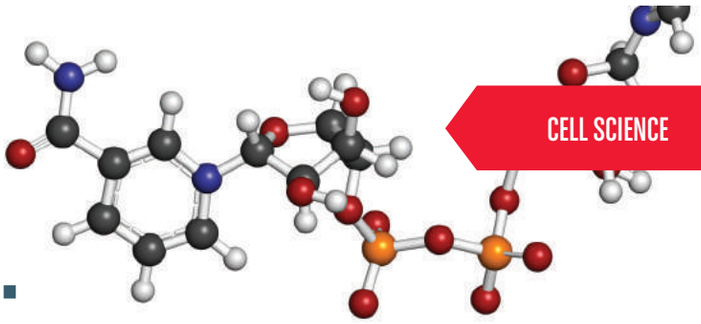

UPDATE ON SIRTUINS:
IS THERE ANY CLINICAL RELEVANCE?

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ABSTRACT

Several studies have shown that the overexpression of sirtuins is associated with increased maximum lifespan in various model organisms, like the budding yeast *Saccharomyces cerevisiae*. Mammalian sirtuins were found to share homology with the yeast *Sir2,* causing gerontologists worldwide to wonder whether sirtuins could also influence ageing in humans. Increasing evidence suggests that sirtuins are implicated in cancer and metabolic, cardiovascular and neurodegenerative diseases.

INTRODUCTION

It has been over fifteen years since the Silent Information Regulator 2 (*Sir2*) gene was shown to extend the lifespan of the budding yeast *Saccharomyces cerevisiae.*[1,2] Since then, studies have been published showing that *Sir2* and its homologs, collectively known as sirtuins, are present in most organisms, including bacteria, plants and animals. In fact, they have been well conserved throughout evolution from archaebacteria to eukaryotes.[3] In evolutionary terms, conservation reflects functional significance, which is why gerontologists worldwide have been trying to understand how these sirtuins function at the cellular, molecular and organismal levels to alter mammalian physiology. For instance, discovering that they can perform nicotinamide adenine dinucleotide (NAD+)-dependent deacetylation reactions[4] opened up a new door of investigation into the metabolic control of sirtuins. Overall, it was shown that lifespan extension through the activation of sirtuins can be done either by calorific restriction or through pharmacological means. Theoretically, this, together with their wide range of activities, suggests that sirtuins could potentially be used as therapeutic targets to combat metabolic, neurodegenerative and age-associated human diseases.[5,6]

DISCUSSION

MAMMALIAN SIRTUINS AND THEIR CLINICAL RELEVANCE

Since *Sir2* was shown to enhance longevity in lower invertebrates, researchers started wondering whether sirtuins also influence ageing in mammals. In the latter, seven sirtuin proteins (SIRT1 to 7) were found to share homology with *Sir2.*[3] Of these, SIRT1 is the proto-member and the most commonly studied mammalian sirtuin. It modifies histones through deacetylation of lysine at position 26 in histone 1 (H1K26), K9 in histone H3 (H3K9) and K16 in histone H4 (H4K16). SIRT1 also deacetylates non-histone proteins that are involved in apoptosis, calorie restriction, cell growth, cell senescence, neuronal protection, organ metabolism and function, and tumourigenesis. In this review, most of the examples will be given on SIRT1 and its involvement in age-related diseases such as **cancer, metabolic**, **cardiovascular** and **neurodegenerative diseases**. However, it is important to note that most of the mammalian sirtuins are involved in a broad range of processes, including ageing, apoptosis, circadian clocks, energy responses to low calorie availability, inflammation, mitochondrial biogenesis, and stress resistance.

Roles of Sirtuins in Cancer and Metabolic Disorders:

Most cancers are characterised by **genomic instability** and **altered metabolism**. Metabolic reprogramming is involved in the response to cellular DNA damage. Therefore, defining the molecules that tune metabolism in response to DNA damage would help to better understand the mechanisms of carcinogenesis. Several studies suggest that the best characterised sirtuin, SIRT1, is a tumour suppressor which improves genomic stability.

However, controversy regarding the role of SIRT1 in cancer exists, since it appears to be bifunctional, operating both as a tumour suppressor and as a tumour promoter, depending on the context and its targets in specific cancers or specific signalling pathways. Evidence for SIRT1's promotion of tumour development and progression revolves around its function as a deacetylase where it acts to suppress the functions of tumour suppressors such as p53. Silencing of these tumour suppressors then prevents cell senescence and DNA damage-induced apoptosis from occurring, therefore allowing cells to proliferate and survive. On the other hand, SIRT1 may also act by suppressing tumour growth; this it does by suppressing NF-κB, a transcription factor with a role in the regulation of tumourigenesis, the dysregulation of which leads to tumour malignancy.[7]

Setting this controversy aside, the roles of sirtuins in maintaining genomic stability have been described as regulators of DNA repair pathways. Oberdoerffer *et al.*,[8] for instance, showed that in response to DNA damage, SIRT1 is recruited to DNA double strand breaks (DSBs); this recruitment is essential for the accumulation of DNA damage response proteins such as BRCA1, NBS1 and Rad51. BRCA mutations are the main known hereditary factors for ovarian cancer. Recently, Li *et al.*[9] highlighted crosstalk between BRCA1 and SIRT1 which may be beneficial for the balance between processes related to BRCA1 and SIRT1-related energy metabolism and stress responses. In addition, when DNA DSBs occur, SIRT1 promotes DNA repair by deacetylating WRN, a helicase important in maintaining genomic stability. SIRT1 is also involved in non-homologous end joining DNA repair. Upon UV damage, a different repair mechanism is involved, specifically, the nucleotide excision repair (NER) mechanism. SIRT1 can regulate

NER by deacetylating and activating xeroderma pigmentosum A and C proteins. When deacetylated, these proteins recognise single stranded DNA binding proteins and recruit other NER factors at the breaks so as to initiate DNA repair.[10] Seeing how sirtuins possess dual roles in DNA repair and metabolism, they can serve as central points in regulating both processes. Indeed, a recent realisation is that DNA damage can trigger metabolic responses, therefore indicating that these two biological entities may function in a coordinated fashion.

It is because of their dependency on NAD+ that sirtuins are thought to play a regulatory role in metabolic pathways. Given its involvement in adipogenesis, fat mobilisation, gluconeogenesis, glycolysis and insulin secretion, SIRT1 has also been implicated in calorie restriction and in insulin resistance at different metabolic tissues. Chen *et al.*[11] showed that mice lacking SIRT1 fail to show increased activity in response to calorie restriction. Recent data has also indicated that the activation of SIRT1 improves the insulin sensitivity of adipose tissues, liver and skeletal muscle, and that it also protects the cell mass and function of pancreatic beta-cells. Such findings point towards SIRT1 as a potential therapeutic target for the prevention of diseases such as metabolic syndrome and type 2 diabetes mellitus.[12]

Roles of Sirtuins in Cardiovascular Diseases:

SIRT1-4 were found to regulate the activities of several coregulators, enzymes and transcription factors that improve metabolic control in adipose tissue, liver, pancreas and skeletal muscle, especially during ageing and obesity. Through the deacetylation of forkhead box O1 (FoxO1) and p53, SIRT1 and SIRT7 have the ability to control myocardial development, and also, resist myocardial dysfunction associated with ageing and stress. In addition, by regulating the expression of angiotensin II type 1 receptor, and the activity of FoxO1, endothelial nitric oxide synthase and p53, SIRT1 can promote regenerative and vasodilatory functions, particularly in the endothelial and smooth muscle cells of the vascular wall. SIRT3 protects cardiomyocytes from ageing and oxidative stress, and together with SIRT6, it also acts to attenuate cardiac hypertrophy. SIRT7 was found to regulate apoptosis and stress responses in the heart.[13] Given that the activation of sirtuins has such a potentially beneficial effect on cardiovascular health, the interest in developing specific sirtuin agonists is corroborated. Moreover, because their activity depends on the availability of NAD+, enzymes involved in the biosynthesis of NAD+, including nicotinamide phosphoribosyltransferase, may also be valuable targets for the management of cardiovascular disease.

Roles of Sirtuins in Neurodegenerative Diseases:

SIRT1 and SIRT2 have been found to be associated with age-associated brain disorders. In animal models, overexpression of SIRT1 protects against amyloid-beta plaque formation. Overexpression of SIRT1 was also shown to suppress the formation of alpha-synuclein aggregates, a characteristic of pathological conditions such as Parkinson's disease and dementia with Lewy bodies.[14] Knocking out SIRT1 in a mouse model of Huntington's disease aggravated the pathology of the brain, whereas its overexpression improved survival and neuropathology.[15] Due to its ability to deacetylate FOXO3, SIRT2 was found to increase the expression of the antioxidant mitochondrial superoxide dismutase. It is widely accepted that oxidative stress is connected to neurodegenerative diseases.[16]

Sirtuin-Activating Compounds (STACs):

STACs are molecules that potentially can be used for the treatment of ageing and age-associated diseases.[17,18] Studies have indicated that both natural and synthetic STACs work to stimulate the activity of sirtuins. Resveratrol, a SIRT1 activator, is perhaps the most eminent STAC. Companies, such as Sirtris Pharmaceuticals, Inc., used to develop STACs, with its lead candidates being SRT2104 and SRT2379, both of which are potent activators of SIRT1. However, controversies behind this 'longevity' company led to its shutdown.

CONCLUSION

Sirtuins affect many biological substrates and the identification of the molecular players involved and their networks is still under intensive research. Surely, when the safety and efficacy of sirtuin modulators have been worked out, they will eventually find their place in the treatment of age-associated diseases.

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