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Pathophysiology of NAMPT in the progression and suppression of heart related diseases

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Abstract

Nicotinamide phosphoribosyltransferase (NAMPT) is an important enzyme that catalyzes nicotinamide adenine dinucleotide (NAD) biosynthesis. NAMPT and NAD are vital for maintaining cellular redox homeostasis and modulation of cellular metabolism. However, the role of NAMPT in the pathophysiology of heart related diseases is not clearly understood but different researchers have over the years tried to explain the actual role of NAMPT in the occurrence of heart diseases. High-circulating levels of NAMPT are reported in different pathological conditions. Extracellular NAMPT is a proinflammatory cytokine that has attracted a considerable attention recently with respect to induction of cardiovascular diseases. Furthermore, studies have also revealed that NAMPT play a very important role in combating NAD depletion in the presence of NAD consuming enzymes, hence preventing the onset of pathological cardiac hypertrophy. This review further explained in detail the role of NAMPT in the progression and suppression of heart diseases as well as cardiovascular diseases.

Keywords: NAMPT; Heart; Disease; Progression; Suppression

1 Introduction

Nicotinamide phosphoribosyl transferase is an important coenzyme that plays a vital role in redox reactions occurring in the cells [1]. It exists in two forms. Inside the cell, NAMPT (iNAMPT) catalyzes the rate-limiting step in the salvage pathway for nicotinamide adenine dinucleotide (NAD+) biosynthesis and thereby regulates the deacetylase activity of sirtuinsand outside the cell (e NAMPT), it functions as a proinflammatory cytokine [1].

High-circulating levels of NAMPT are reported in different pathological conditions. eNAMPT is a proinflammatory cytokine that has attracted a considerable attention recently with respect to induction of cardiovascular diseases. Its role as an enzyme and cytokine makes it unique among the group of cytokines [1].

2 NAMPT is an NAD+-regenerating Enzyme

In mammals, the role of NAMPT as a NAD-synthesizing enzyme is vital in combating stress since severe stress can lead to NAD depletion owing to direct loss of NAD from cells or because of elevated activity of NAD-consuming enzymes like poly (ADP-ribose) polymerase, sirtuins, and cyclic-ADP ribose synthases. This is vital in the setting of cardiac hypertrophy because pathological hypertrophy is associated with reduced levels of (NAD) [2]. Thus, NAMPT (iNAMPT) works inside the cell to maintain intracellular NAD levels and hence partake in the regulation of the activity of several enzymes involved in mediating stress resistance,cell survival and control of metabolism [3]. NAMPT, like many other

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cytokines is released into circulation by a variety of cell types including fetal membranes, adipose tissue, lymphocytes and liver [3].

Elevated levels of circulating NAMPT were reported in different clinical conditions, such as obesity, type 2 diabetes, and chronic inflammatory diseases [3].

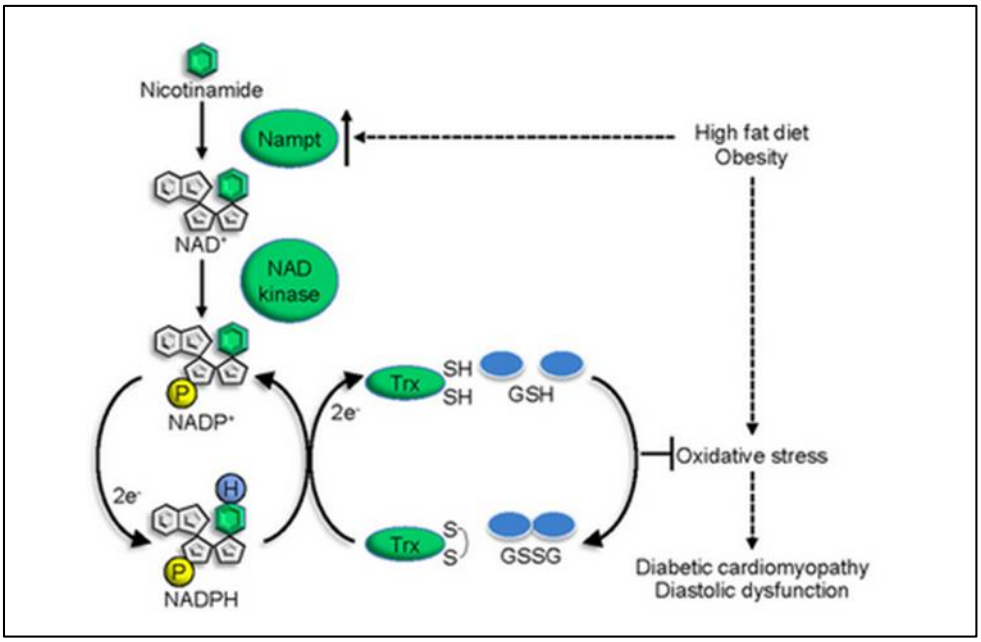
There is a strong correlation between NAMPT expression and atherosclerosis [4]. Studies revealed that NAMPT induced endothelial dysfunction and contribute to destabilization of atheromatous plaque. Patients with coronary artery disease were reported to have increased epicardialNAMPT levels, compared with control subjects [5]. The direct effect of NAMPT in the heart has been explained by three studies. In the analysis by Lim et al., (2008) it was reported that addition of NAMPT at the time of myocardial reperfusion significantly reduced myocardial infract size. Similarly, cardiac-specific expression of NAMPT reduced myocardial infract size in response to prolonged ischemia and ischemia-reperfusion injury.On the contrary to these findings, inhibition of NAMPT reduced neutrophil-mediated injury in myocardial infarction [6].

3 NAMPT promotes cardiac hypertrophy

Vinodkumar*et al.* (2013) reported that cardiac-specific expression of NAMPT promotes cardiac hypertrophy and dysfunction. In the study NAMPT-Tg (Transgenic-NAMPT) mice produced nearly 25% cardiac hypertrophy which was associated with accumulation of fibrosis in the interstitial space. NAMPT-Tg mice showed significantly decreased Left Ventricular fractional shortening and elevated wall thickness. It was also reported that NAMPT-Tg mice showed reduced capillary density compared with control mice as revealed by decreased CD31 staining. These results suggest that NAMPT-Tg mice spontaneously develop pathological cardiac hypertrophy [3].

4 NAMPT promotes Antioxidant Defense in Diabetic Cardiomyopathy

Increase in production of NADH in diabetic cardiomyopathy, through fatty acid oxidation and consequent increase in oxidative stress is a major center of focus in determining the role of NAMPT [7]. However, the role of NAMPT, the rate-limiting enzyme of the salvage pathway of nicotinamide adenine dinucleotide synthesis, in the proliferation of diabetic cardiomyopathy is not well understood.



Shin-ichi, O., Jaemin, B., Chun-yang, H., Nobushige, I., Guersom, R., Peiyong, Z., Xiaoyong, X., Sanchita,K.,Junco, S. W., John, A. M., Trevor,S. T., Mingming, T., Sundararajan, V., Yoshiyuki, I., Wataru, M., Toshihide, K. and Junichi, S. (2021). NAMPT Potentiates Antioxidant Defense in Diabetic Cardiomyopathy Circulation Research. 129:114–130.

Figure 1 Potentiation of Antioxidant Defense in Diabetic Cardiomyopathy by NAMPT

NAD^+ production mediated by NAMPT protects against oxidative stress, in part, through the NADPH-dependent reducing system, thus eliminating the development of diabetic cardiomyopathy in response to high fat density (HFD) consumption [7].

5 NAMPT regulates NAD+ levels in the heart

At baseline there is a significant decrease in NAD+ content in cardiomyocytes when NAMPT is downregulated, suggesting its crucial role in NAD+ synthesis in cardiomyocytes [8]. On the other hand, overexpression of NAMPT readily increases NAD+ content, indicating that NAMPT is a rate-limiting enzyme for NAD+ synthesis in cardiomyocytes [8]. Under stress conditions in the heart, NAMPT is downregulated at both the protein and mRNA levels, including 24 hours of ischemia, 45 minutes of ischemia followed by 24 hours of reperfusion, and 2 and 4 weeks of pressure overload due to thoracic aortic constriction [8] which facilitate compensated and decompensated stages of cardiac hypertrophy, respectively in mice. These changes are accompanied by decreases in the level of NAD+ in the heart [2]. These results suggest that NAMPT is a critical determinant of the NAD+ level in the heart at baseline and in response to stress [9].

6 NAMPT protects the heart against ischemia/reperfusion (I/R) injury

In a mouse model of ischemia-reperfusion study, an administration of intravenous NAMPT at the time of myocardial reperfusion reduced the myocardial infract size [14]. It was reported by Hsu et al. that the size of the myocardial infarct/area at risk was significantly smaller in Tg-NAMPT than in NTg (normal transgenic) mice upon myocardial I/R injury.Since endogenous NAMPT is down-regulated by I/R and cardiac-specific over-expression of NAMPT restores the NAD+ level [8], these results suggest that downregulation of endogenous NAMPT contributes to myocardial injury in response to I/R and that upregulation of NAMPT protects the heart against I/R injury. Also it was shown that NAMPT has cell-autonomous and protective effects against cell death in cardiomyocytes. In the study overexpression of NAMPT protected cardiomyocytes from cell death induced by either methylmethanesulfonate, a DNA-alkylating agent known to induce necrotic cell death, or glucose deprivation. On the other hand, downregulation of NAMPT significantly increased apoptotic cell death in cardiomyocytes, as evaluated with TUNEL staining and immunoblot analyses of cleaved caspase-3 [10].These results suggest that NAMPT directly regulates apoptosis in cardiomyocytes. Under physiological conditions growth factors are also associated with protection of cells from stress [13], the immediate effect of NAMPT would be safe guarding cardiomyocytes from oxidative stress and apoptosis [3].

7 NAMPT Axis Suppresses Atrial Fibrillation

Atrial fibrillation is a heart condition that leads to an irregular and often abnormally fast heart rate. It is characterized by irregular atrial electrical activity resulting in asynchronous atrial contraction [11]. Atrial fibrillation increases the risk of heart failure, embolic stroke and overall mortality [12]. According to study by Duo et al., (2020), it was observed that partial deletion of NAMPT facilitated high fat density induced atrial fibrillation through increased diastolic calcium leak, suggesting that NAMPT/NAD axis may be a potent therapeutic target for atrial fibrillation.

8 NAMPT regulates cardiac fibroblast proliferation and differentiation.

The activation of cardiac fibroblast proliferation and their transformation into myofibroblasts is an important component of myocardial remodeling [3]. Vinodkumar et al. investigated the effect of NAMPT on cardiac fibroblast proliferation, differentiation, and apoptosis. It was discovered that NAMPT increased cardiac fibroblast proliferation, which was inhibited by NAMPT-blocking antibody and the increase in Smooth muscle actin and collagen 1 after NAMPT treatment suggests that NAMPT promotes myofibroblast differentiation.

9 NAMPT in Cardiovascular diseases

NAMPT have been proposed as a marker of atherosclerosis. Increased expression of NAMPT in the periaortic and pericoronary fat of patients with coronary atherosclerosis condition suggests its potential paracrine role in the development of atherosclerotic lesions [15]. Study revealed the up regulation of NAMPT in the site of plaque rupture in patients with acute myocardial infarction as well as in plaques formed in the carotid artery of patients with symptoms of stroke [16]. Elevated levels of NAMPT were also found in the abdominal and epicardial fat tissues of coronary heart disease patients, suggesting a positive correlation between NAMPT and cardiovascular diseases [17].

10 Conclusion

NAMPT is an important cytokine as well as growth factor with a unique ability to synthesize NAD. Studies have revealed that continuous release of NAMPT to the heart is capable of causing cardiac disorders and failure. Regulation of NAMPT flow to the heart can help limit the progression of heart related disease caused by excess NAMPT.

Compliance with ethical standards

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Disclosure of conflict of interest

The Authors declared no conflict of interest.

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