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A Review on the Role of Nicotinamide Phosphoribosyl Transferase in the Adipose Tissue

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Abstract:- NAMPT has recently attracted a lot of concern in various domains like NAD biology, inflammation, and metabolism. NAMPT is vital in the biosynthesis of NAD+ which is essential in the metabolism of energy in different organisms; and modifies the effect of NAD-consuming enzymes like sirtuins. The combined effect of NAMPT-mediated NAD+ biosynthesis and SIRT1 is paramount in regulating various biological mechanisms such as metabolism, cellular differentiation, stress response, and circadian rhythm and mediating conformational responses to restricted energy consumption like fasting and limited diet. Though, a defect in adipose NAMPT-mediated NAD+ production results in significant multi-organ insulin resistance, which is a consequence of obesity-related systemic metabolic dysfunction. In metabolic syndromes like T2D, polycystic ovarian syndrome, or gestational diabetes NAMPT level is usually elevated. As a result, this review focuses on the role of NAMPT in the adipose tissue, since it's a major ground for eliciting its activities.

I. INTRODUCTION

Nicotinamide Phosphoribosyltransferase (NAMPT), on discovery in 1994 was called a pre-B-cell colony enhancing factor (PBEF) produced by bone marrow stromal cells and activated lymphocyte presume to strengthen the maturity of B-cell ancestors [1], and as a visfatin, an adipokine obtained from visceral fat presume to mimic insulin action by interacting with the receptor. However, neither of the functional effects of PBEF or visfatin has been reaffirmed [2]. Rather, NAMPT was acknowledged as the gene and protein's official name by both the HUGO Gene Nomenclature Committee and the Mouse Genomic Nomenclature Committee [3]. Notwithstanding, in the production of NAD+, NAMPT catalyzed the slowest step, and act intracellularly to convert 5'- phosphoribosyl-1-pyrophosphate (PRPP) and nicotinamide into the intermediate, nicotinamide mononucleotide (NMN) which is then converted to NAD+ by nicotinamide mononucleotide adenylyltransferases 1 to 3: (NMNAT1 in the nuclear), (NMNAT2 in the golgi complex and cytosol), (NMNAT3 in the mitochondrial or cytosol the major source of adipose NAD+) [4,2,11]. Nevertheless, activated lymphocytes, monocytes, and neutrophils in humans secrete NAMPT homologs, which have also been found in invertebrate mollusks, carp, bacteria, and mice [5]. In the metabolism of energy in several organisms, nicotinamide adenine dinucleotide (NAD+) is crucial. And can be produced from nicotinic acid, nicotinamide riboside (NR), nicotinamide the major source of NAD+ in mammals, and tryptophan. [2,4,3]. However, in adipocyte biology, novel research indicates that adipose tissue performed endocrine functions in its ability to manufacture and secretes various factors (adipocytokines) such as leptin, adiponectin, tumor necrosis factor–α (TNF-α), free fatty acids (FFAs), and plasminogen activator inhibitor–1 interleukin-6 (IL-6) which are capable of greatly influencing metabolic homeostasis of the entire body and promotes the etiology of atherosclerosis, insulin resistance[1,5,21], dyslipidemia and inflammation [3]. consequently, a high amount of NAMPT is observed in the neutrophils of patients with septic shock, synovial tissue of rheumatoid arthritis patients, and in the macrophage of irregular atherosclerotic plaques, its proinflammatory marker in macrophages found in adipose tissue and upregulate inflammatory genes of TNF-α, interleukin-8, IL-6 expression in monocytes [6], animates the reflection of IL-6 and IL-8 in amniotic cells, and protract survival of neutrophil in clinical sepsis [5]. According to research, NAMPT levels rise in people with metabolic syndrome, T2D, polycystic ovarian syndrome, or gestational diabetes. Again, macrophage infiltration in adipose tissue is an inferior state of inflammation that is associated with SAT and VAT NAMPT mRNA expression. The link between insulin resistance and NAMPT may be mediated by increased adipose tissue inflammation. [6].

II. NAMPT IN ADIPOSE TISSUES

NAMPT has adipokine properties, immune system cytokine effects, and affects how much energy is stored in adipose tissue. [7]. Its functions contribute to both the peripheral and central regulation of systemic metabolic homeostasis in murine [14]. NAMPT attaches to insulin receptors at a distinct position from that of insulin, and stimulates the insulin signal transduction pathway by inducing phosphorylation of signal transduction proteins in the insulin signaling pathway [8] to trigger 'insulin-mimicking' action, stimulate triglyceride synthesis (TGS) and glucose transport (GluT) [7]. However, two types of NAMPT are found in animals: intracellular (iNAMPT) and extracellular (eNAMPT) [2]. iNAMPT is crucial in the NAD biosynthetic pathway, and it is abundantly expressed in mice's liver, brown adipose tissue (BAT), and kidney; moderately expressed in the heart; lowly expressed in the lung, white adipose tissue (WAT), spleen, skeletal muscles, and testis; and a trace amount in the brain and pancreas. [9]. eNAMPT, on the other hand, is secreted by

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matured white and brown adipocytes with 2-4 times the enzymatic activity of iNAMPT, and its secretion and enzymatic actions are modulated by SIRT1-dependent deacetylation in adipocytes in response to fasting. As a result, decreasing glucose promotes the secretion of eNAMPT by 3.5 to 5.5 folds in matured HIB-1B brown and 3T3-L1 white adipocytes [2]. Interestingly, by making NAD+ available for SIRT3 to activate Acetyl-coenzyme A synthase (ACS), NAMPT is crucial for the formation of acetyl coenzyme A (a precursor to palmitic acid) [10]. NAMPT, a protein with pleiotropic properties, may work as the second NAD-biosynthetic enzyme (NBE) known as nicotinate phosphoribosyltransferase (NAPRT), a growth factor, cytokine, and adipokine.[1], modulate sirtuins (SIRT) and poly (ADP-ribose) polymerase (PARPs) which are vital NAD+-consuming mediators [4]. Moreso, the concerted action of NAMPT-mediated NAD+ production and SIRT1 are vital in regulating various biological mechanisms such as metabolism, cellular differentiation, stress response, and circadian rhythm and mediating conformational responses to restricted energy consumption, like fasting and limited diet [9]; For instance, In the presence of glucose, the NAD+ production mediated by SIRT1 and NAMPT controls glucose-stimulated insulin secretion (GSIS) in pancreatic β cells, as well as in the white adipose tissue (WAT) and liver; being a potent metabolic effector, NAMPT and SIRT1 together form a transcriptional-enzymatic feedback loop for modifying circadian rhythm[9]. Nonetheless, altered mitochondrial protein homeostasis, insulin resistance, acquired obesity, and inflammation in SAT are connected with repression in the expression of the NAD+/SIRT pathway [11]. According to Beltowski et al study, plasma insulin levels were unaffected by the acute intravenous NAMPT delivery, which decreased plasma glucose concentration, thus suggesting that NAMPT hypoglycemics action is not via an insulin-stimulating mechanism [12]. Still, as an adipocytokine, NAMPT contributes to the onset of diabetes mellitus and the insulin resistance linked with obesity [12,21]. Compared, to subcutaneous fat, it is mostly expressed in the visceral fat of both humans and animals. Though, it is usually elevated in the obese. Accordingly, plasma NAMPT level correlates strongly with visceral fat in humans [5,12]. Notwithstanding, in the adipose tissue of obese mice, the expression of NAMPT mRNA is upregulated; additionally, human subject with T2D and visceral-fat accumulation presents increased NAMPT serum level. Likewise, In vitro NAMPT administration amplified Akt and IRS-1 phosphorylation along with glucose absorption in adipocytes and osteoblasts; increased the expression of IL-8 and TNF-a in monocytes using the insulin receptor signaling pathway [13]. howbeit, studies have shown that diet, environment, age, and obesity control the adipose tissue's NAMPT-mediated NAD+ production; for instance, NAMPT protein and NAMPT mRNA expressed in adipose tissue display vital diurnal swing, while diets restriction results in the elevation of NAMPT protein, NAMPT mRNA and NAD+ quantity in adipose tissue. Conversely, diet or genetic-induced obesity caused a reduction of NAMPT and NAD+ content in adipose tissue and depressed diurnal oscillation of gene expression [4]. Also, aging or hepatosteatosis-induced inflammation or/and oxidative stress initiate the decrease in NAMPT-mediated NAD+ production and encourage the development of T2D; though the NAD+ intermediate NMN is capable of reversing the pathological effect of diet and age induce T2D and nullify the effects of oxidative stress, circadian rhythm, and inflammatory response on gene expression [9]. Moreover, in insulin-resistance individuals, the NAMPT gene and NAMPT protein content decreased, compared to insulin-sensitive individuals; in obese and overweight individuals, diet-induced weight loss elevates NAMPT gene expression in adipose tissue [4]. Nevertheless, the study by Nielson et al revealed that adipose tissue lacking NAMPT is protective against diet-induced obesity and enhances glucose tolerance. Therefore, NAMPT in adipose tissue facilitates weight gain in response to dietary fat [14]. Howbeit, healthy adipose tissue exhibits strong flexibility, growing and shrinking in size and adipocyte number depending on nutrient availability; NAD+ generation in the adipocytes is required for the physiological expansion and contraction of white adipose depots under high-fat diets because it may be particularly crucial in controlling lipid buildup. Wherefore, NAMPT is critical in adipose plasticity specifically in coping with dietary fat [14].

III. NAMPT AND METABOLIC FUNCTIONS

NAMPT-mediated NAD+ production from adipose tissue is essential for controlling the body's entire metabolic process as evidenced by the study of Stromsdorfer et al. whereby deletion of adipose-specific NAMPT caused impairment of adipose tissue, defined by a reduction in the synthesis of essential adipokines such as adiponectin and adipsin, plasma free fatty acid (FFA) acceleration, inflammation of local adipose tissue; high insulin resistance in the liver, skeletal muscle, and adipose tissue without a concurrent body weight or adipose tissue increased; increased phosphorylation of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARɣ) and cyclin-dependent kinase 5 (CDK5), a vital regulator of PPARɣ phosphorylation at Ser273, decreased depiction of the gene associated with obesity-link specific targets of PPARɣ phosphorylation including adipsin and adiponectin. However, administration of PPARɣ agonist rosiglitazone, NAD intermediate NMN, or NAD precursor NA normalized these adverse metabolic effects. Thus, a defect in adipose NAMPT-mediated NAD+ production results in significant multi-organ insulin resistance, which is a consequence of obesity-related systemic metabolic dysfunction [4]. PPARɣ, an adipogenic factor is majorly expressed in adipose tissue and known to regulate the expression of genes concerned with lipid metabolism, and its activation is associated with increased differentiation of adipocytes with amplified ability to receive and store lipids thereby enhancing insulin sensitivity in other tissues [12]. Strikingly, NAMPT is elevated by peroxisomal proliferator-activated receptor (PPAR)- α and PPARɣ agonists in obese

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rats in conjunction with enhanced glycaemic regulation and lipid profile, implying that PPARУ and PPARα agonists could act in part via the elevation of NAMPT expression [15]. Besides, NAMPT induces triglyceride accumulation, stimulates differentiation of preadipocytes into matured fat cells, enhanced the production of triglycerides from glucose, and induces the expression of genes encoding the adipose tissue-specific indicators peroxisome proliferator-activated receptor-y (PPARУ), diacylglycerol acyltransferase fatty acid synthase, and adiponectin [12]. However, In the study by Sun et al., injection-induced generation of excess NAMPT resulted in higher PPARУ mRNA manifestation in the liver and adipose tissues, improved systemic insulin sensitivity, and decreased levels of circulating cholesterol. Because of this, it's probable that NAMPT altered PPARУ activity to reduce insulin sensitivity and lipid profile [12]. Although, visceral fat along with insulin resistance promotes abnormal lipid metabolism [16]. and in human adipose tissue, the expression of the NAMPT gene is closely linked to that of CD68, a macrophage-specific marker, and proinflammatory genes. This association increases systemic insulin resistance and upregulates plasma triglyceride and total cholesterol levels. Consequently, NAMPT is an adipose tissue pro-inflammatory marker linked to insulin resistance and hyperlipidemia [17]. Studies have shown that people with type 2 diabetes (T2DM), extended type 1 diabetes, and obese children all have plasma concentrations of NAMPT that are two times higher than the average (T1DM). Additionally, Progressive degeneration of β-cells has been linked to a higher NAMPT level [18]. And in the leukocytes of obese patients, the level of NAMPT is higher compared to the lean individuals, which correlates with an elevated NAMPT secretion from adipose tissue-derived macrophages [19]. Again, male humans' body mass index (BMI) and body fat percentage have been shown to be correlated with NAMPT [15]. Similarly, the amount of VAT NAMPT mRNA is positively associated with plasma triglyceride and total cholesterol; circulating NAMPT concentration was seen to increase with plasma triglyceride of young healthy men, and obese children and with an elevation of LDL-C among those with metabolic syndrome [6]. VAT is highly connected to insulin resistance [15,8] In insulin-deficient diabetic mice, NAMPT reduces hyperglycemia just as well as insulin [5]. The Study by Wang et al. revealed that in non-diabetic Caucasian subjects, the plasma NAMPT concentration correlated with HDL-cholesterol and low triglyceride. And the obese individuals that possess a lower concentration of plasma NAMPT presented lower HDL-cholesterol and higher triglyceride compared to lean individuals [16]. Also, oral nicotinamide treatment dramatically raises cellular NAD levels and serum HDL cholesterol levels in people receiving hemodialysis. Additionally, nicotinic acid, a different substrate for NAD production, has been touted as the most effective HDL-cholesterol-raising substance. However, the benefit of high HDL cholesterol and low plasma triglycerides, however, may be related to NAD metabolism since the change in HDL cholesterol is strongly correlated with the change in NAD levels throughout the blood cell. And the relationship between circulating NAMPT and plasma lipid profile indicates that NAMPT may serve as a medium for those two processes [16]. The high-fat diet reduces Sirt1, Sirt3, and NAMPT transcription and induces PARPs which majorly consume the intracellular NAD+ pool [11]. Also, Obese mice devoid of tumor necrosis factor (TNFα) or its receptor are immune to insulin resistance, which supports the fact that TNFα plays a role in the relationship between obesity and insulin resistance [20]. Strikingly, TNF-a downregulates NAMPT expression in 3T3 adipocytes and decreases glucose transporter GLUT4 mRNA in adipocytes [7]. The protracted effects of transcriptional modulation of important adipocyte differentiation regulators, such as peroxisome proliferator-activated receptor У (PPARУ) and CAAT/enhancer binding protein α (C/EBPα), as well as regulation of the expression of adipokines like adiponectin, leptin, and interleukin 6 (IL-6), that intensively affect insulin sensitivity, are what cause TNF-dependent insulin resistance [20]. A study has reported TNFα to be a vital disruptor of insulin signaling, as its administration in 3T3-L1 adipocytes resulted in the decrease of NAMPT gene expression and its intracellular protein levels, downregulated NAD+ concentration resulting in reduced Sirt1 activity which is NAD+ dependent; also, inhibition of Sirt1 in adipocytes resulted in the downregulation of insulin sensitivity and prevented insulin-stimulated glucose transport in adipocytes specifically by obstructing insulin signaling. Thus, as a reduction in NAD+ consequently decreased Sirt1 activity, NAMPT could be linked to insulin sensitivity. However, this is controversial being that in the human study, an inverse correlation between NAMPT and TNFα plasma concentration has been observed [20]. TNFα prevents tyrosine residues from being phosphorylated by the insulin-stimulated insulin receptor (IR) and insulin receptor substrate 1 (IRS-1) [22] by preventing phosphorylation of IRS-1 serine 307, activation of jun amino-terminal kinase (JNK1) and protein kinase C-θ [23], inducing suppressor of cytokine signaling (SOCS) proteins [24] and turning on protein-tyrosine phosphatase 1B (PTP1B), a suppressor of insulin signaling and a contributor to the inflammatory response. And excess expression of PTP1B in vitro in hepatic and muscles cells manifested in the reduction of IR and IRS-1 tyrosine phosphorylation, and subsequently decrease glucose uptake; according to reports, PTP1B contributes to TNF-mediated insulin resistance, conversely, Sirt1's ability to inhibit PTP1B transcription in skeletal muscles is another way it can improve insulin sensitivity. Reduction in the expression and activation of NAMPT resulted in lowering intracellular NAD+ concentrations and upregulation of PTP1B expression via Sirt1 activity [20].

IV. CONCLUSION

Through sirtuins and other NAD-consuming modulators, NAMPT works as an intra- and extracellular NAD biosynthesis enzyme that is crucial for controlling metabolism and stress resistance. However, people with type 2 diabetes (T2DM), extended type 1 diabetes, Progressive β-cells

degeneration, and obese children all have high plasma NAMPT compared to the average (T1DM). Although, in insulin-resistance individuals, the NAMPT gene and NAMPT protein content decreased, compared to insulin-sensitive individuals. Diet-induced weight loss increased the level of the NAMPT gene expressed in the adipose tissue of the obese. Howbeit, knowledge of the therapeutic approach to countering these pathophysiological impacts of NAMPT in metabolic function is poor and therefore, required further research to ensure an optimum NAMPT level after a shift in an abnormal condition.

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