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Chapter 5

Nicotinamide Phosphoribosyltransferase in Sepsis

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1. Introduction

The word sepsis was derived from the Greek word: sêpsis, which means the state of putrefaction or decay. Sepsis is a potentially deadly medical condition that is characterized by a whole-body inflammatory state, called a systemic inflammatory response syndrome, and the presence of a known or suspected infection. The more critical subsets of sepsis are severe sepsis with acute organ dysfunction, hypoperfusion, or hypotension and septic shock with refractory arterial hypotension despite adequate fluid resuscitation [1, 2]. Because the molecular pathogenesis of sepsis is incompletely understood and its specific and effective therapies are lacking, sepsis is still a major cause of death in intensive-care units worldwide, with mortality rates that range from 20% for sepsis, through 40% for severe sepsis, to over 60% for septic shock [3, 4]. More knowledge of the pathophysiology of sepsis is needed if we are to develop better, more effective interventions to sepsis. It has been increasingly recognized that genetic factors influence individual susceptibility, severity and outcome in sepsis [5, 6]. Identification of new genetic factors in sepsis may hold promise for new mechanistic insights and new therapeutic modalities.

Nicotinamide phosphoribosyltransferase (NAMPT) is emerging as a risk factor in sepsis. NAMPT is a pleiotropic protein. It catalyzes the condensation of nicotinamide with 5-phosphoribosyl-1-pyrophosphate to yield nicotinamide mononucleotide, which is the key step in a salvage pathway of the mammalian NAD biosynthesis[7]. NAMPT was first cloned by Samal et al.[8]and it was originally named pre-B-cell colony enhancing factor (PBEF) because it can promote the maturation of pre-B-cells. NAMPT was also called visfatin because it is an adipokine highly produced by visceral fat and it displayed insulin mimetic functions [9] though the latter claim was disputed in literature. In this chapter, NAMPT and PBEF are used interchangeably in some parts. Jia et al. [10] from University

of Toronto, Canada, first reported that NAMPT mRNA in neutrophils from critically ill septic patients was expressed at higher levels than those in controls. Our previous study at Johns Hopkins University, USA, discovered that a susceptible haplotype GC in the promoter of human NAMPT gene had a 4.84-fold higher risk of sepsis while a potential protective haplotype TT had a lower risk of sepsis in a Caucasian patient population [11]. Bajwa et al. [12] from Massachusetts General Hospital, Harvard University, USA, replicated and extended our findings that the NAMPT-1001T>G variant allele and related haplotype were associated with increased odds of developing acute respiratory distress syndrome (ARDS), which is frequently associated with severe sepsis, and increased hazard of intensive care unit mortality among at-risk patients, whereas the -1535C>T (originally labeled as -1543C>T) variant allele and related haplotype are associated with decreased odds of ARDS among patients with septic shock and better outcomes among patients with ARDS. Molecular mechanisms underlying these associations have been actively explored. The first part of this chapter introduces the physiological functions of the NAMPT gene. The second part of this chapter synopsize the clinical investigation and epidemiological studies of NAMPT in sepsis. The third part describes our current understanding of molecular mechanisms underlying NAMPT in sepsis. The final part of this chapter includes a brief summary and some perspectives on exploring *Terra Ignota* of NAMPT in sepsis.

2. Physiological functions of the NAMPT gene

This section briefly introduces the three major functions of the NAMPT: Growth Factor, Cytokine and Nicotinamide phosphoribosyltransferase [13]. Accumulating evidence suggests that NAMPT can function as a growth factor or a cytokine though the underlying molecular mechanisms remain to be established. It is beyond the dispute that NAMPT can function as a Nicotinamide phosphoribosyltransferase.

Growth Factor. Several studies indicate that NAMPT may function as a growth factor. Samal et al.[8] first found that conditional medium from COS7 or PA317 cells transiently expressing human NAMPT can significantly enhance the number of pre-B-cell colonies derived from normal human or mouse bone marrow by at least 70% in the presence of both IL-7 and stem cell factor. Similar observation was obtained using the antibody purified NAMPT protein. Thus, the authors first named this protein as pre-B-cell colony enhancing factor. Van der Veer et al.[14] reported that NAMPT can promote vascular smooth muscle cell maturation. They found that knockdown of endogenous NAMPT increased smooth muscle cell apoptosis and reduced the capacity of synthetic smooth muscle cells to mature to a contractile state. On the other hand, human smooth muscle cells transduced with the NAMPT gene had enhanced survival, an elongated bipolar morphology, and increased levels of h-caldesmon, smoothelin-A, smoothelin-B, and metavinculin. Fukuhara and co-workers [9] proposed NAMPT as a Visfatin, an adipokine produced by visceral fat that can engage and activate the insulin receptor. Although this publication was retracted because of questions regarding the reproducibility of the NAMPT/ insulin receptor interaction from different preparations of recombinant NAMPT protein[15]. Xie et al.[16] found that NAMPT exerts an

insulin-like activity as a growth factor for osteoblasts. They used the recombinant human NAMPT provided by Axxora Life Sciences (San Diego, CA, USA) in their experiments. They noticed that the effects of NAMPT such as glucose uptake, proliferation, and type I collagen enhancement in cultured human osteoblast-like cells bore a close resemblance to those of insulin and were inhibited by hydroxy-2-naphthalenylmethylphosphonic acid tris-acetoxymethyl ester, a specific inhibitor of IR tyrosine kinase activity. They also unexpectedly found that NAMPT downregulated osteocalcin secretion from human osteoblast-like cells. These data indicate that the regulation of glucose uptake, proliferation, and type I collagen production by NAMPT in human osteoblasts involves insulin receptor phosphorylation, the same signal transduction pathway used by insulin.

Cytokine. NAMPT may be added to the list of cytokines. The first NAMPT cDNA was screened out using a degenerate oligonucleotide probe designed on the basis of the similarity in the coding sequences of five different cytokines: GM-CSF, IL-2, IL-1β, IL-6 and IL-13, at the signal peptidase processing site though the DNA or protein sequence of NAMPT bears no homology to other known cytokines[8]. Ognjanovic et al.[17] reported that lipopolysaccharide, IL-1β, TNF α and IL-6 all significantly increased the expression of NAMPT in a 4 h treatment of the amniotic epithelial cell line, WISH cells. The addition of dexamethasone to IL-1β and TNFα significantly reduced the response to these cytokines. They concluded that NAMPT is a cytokine expressed in the normal fetal membranes and up-regulated when they are infected. NAMPT expression is up-regulated in a variety of acute and chronic inflammatory diseases including sepsis[10], acute lung injury [11], rheumatoid arthritis [18], inflammatory bowel disease[19], and myocardial infarction [20] and plays a key role in the persistence of inflammation through its capacity to inhibit neutrophil apoptosis[10]. rhNAMPT treatment of WISH cells and fetal membrane explants significantly increased IL-6 and IL-8 gene expression[21]. We also found that an overexpression of NAMPT significantly augmented IL-8 secretion and mRNA expression in A549 cells, a human pulmonary carcinoma type II epithelial cell line and human pulmonary artery endothelial cells. It also significantly augmented IL-1β-mediated cell permeability. The opposite results were obtained with the knockdown of NAMPT expression. NAMPT expression also affected the expression of two other inflammatory cytokines (IL-16 and CCR3 genes) [22, 23]. Hong et al.[24] demonstrated recombinant human NAMPT as a direct rat neutrophil chemotactic factor in *in vitro* studies. They also demonstrated a marked increase in bronchoalveolar lavage leukocytes after the intratracheal injection of rhNAMPT into C57BL/6J mice. Thus, NAMPT behaves like a chemokine.

Nicotinamide phosphoribosyl transferase. The clue that PBEF could be a nicotinamide phosphoribosyl transferase was first obtained by the work of Martin et al.[25] in 2001. They demonstrated that the presence of the *nadV* gene allowed *A. pleuropneumoniae* to utilize nicotinamide mononucleotide as a precursor for NAD biosynthesis, and indicate that the enzyme encoded by this gene is a novel NAMPT. They found that the sequence of nadV gene is homologous to that of human NAMPT, suggesting that mammalian PBEF may also function as a NAMPT. Rongvaux et al.[26] verified that similarly to its microbial

counterpart, PBEF is a NAMPT, catalyzing the condensation of nicotinamide with 5-phosphoribosyl-1-pyrophosphate to yield nicotinamide mononucleotide, an intermediate in the biosynthesis of NAD (Figure 1). The role of PBEF as a NAMPT was further confirmed by showing that the mouse gene was able to confer the ability to grow in the absence of NAD to a NAMPT-defective bacterial strain. Study by Revollo et al.[7] demonstrated that NAMPT catalyzes a rate-limiting step in a salvage pathway of the mammalian NAD biosynthesis. Van der Veer et al.[27] proved that it is due to the enhanced NAMPT activity of PBEF that cellular lifespan of human primary smooth muscle cells, human clonal smooth muscle cells, and fibroblasts derived from a patient with Hutchinson-Gilford progeria syndrome can be lengthened. Recent work by Revollo et al [33] revealed that NAMPT regulates insulin secretion in beta cells as a systemic NAD biosynthetic enzyme.

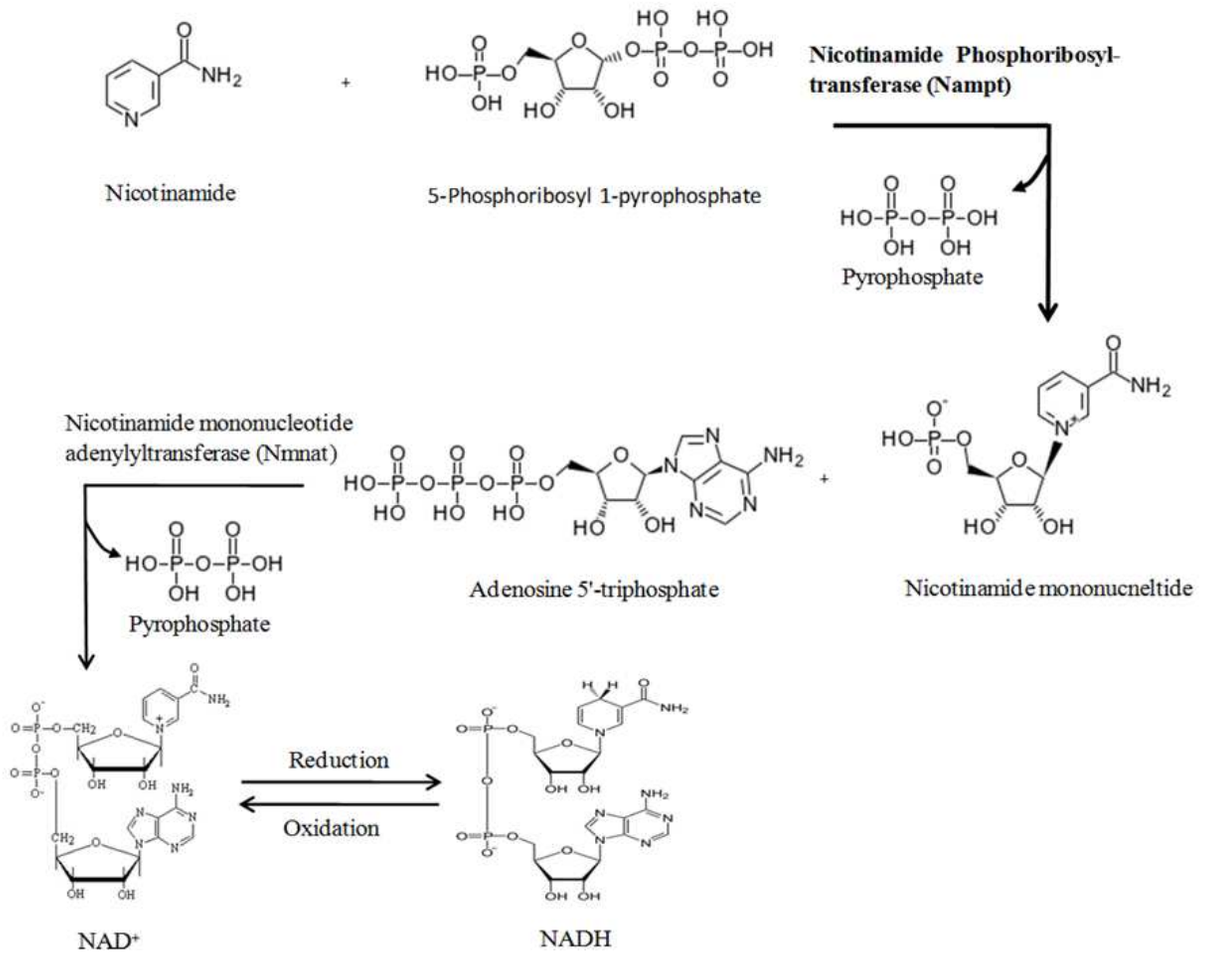

Figure 1. Mammalian salvage pathway of NAD⁺ synthesis mediated by nicotinamide phosphoribosyltransferase. Nicotinamide, either derived from the degradation of NAD⁺ by NAD⁺ consuming enzymes or provided in the diet, is condensed with 5-phosphoribosyl-1-pyrophosphate to yield nicotinamide mononucleotide under the catalysis of nicotinamide phosphoribosyltransferase. Nicotinamide mononucleotide is then adenylylated to form NAD⁺, by Nicotinamide mononucleotide adenylyltransferase. NAD⁺ and NADH can be interconverted by a reduction and a oxidation reaction, respectively. This figure is copied from Zhang et al. (7).

Because the salvage pathway of NAD synthesis is much more efficient and quicker one than that of de novo NAD synthesis, it is conceivable that NAMPT plays an important role in varieties of physiological processes in life via the synthesis of NAD. NAD is now regarded as a universal energy- and signal-carrying molecule[28, 29]. Recent research has unraveled an unexpectedly wide array of signaling pathways that involve nicotinamide adenine dinucleotide (NAD) and its phosphorylated form, NADP. NAD serves as substrate for protein modification including protein deacetylation and mono- and poly-ADP-ribosylation. Both NAD and NADP represent precursors of intracellular calcium-mobilizing molecules. It is now well accepted that NAD (P)-mediated signal transduction does not merely regulate metabolic pathways but might hold a key position in the control of fundamental cellular processes. In mammals, it has been shown recently that an NAD-dependent protein deacetylase, silent information regulator (SIR) T1/2, plays important roles in a variety of biological processes, such as stress and cytokine responses[30], by deacetylating transcriptional regulators. Endogenous mono-ADP-ribosylation in higher eukaryotes appears to modulate the immune response, cell adhesion, signal, and energy metabolism[31]. Recently, defensin-1, an antimicrobial arginine-rich protein secreted by immune cells, was demonstrated to lose its antimicrobial effect after its mono-ADP-ribosylation. Poly-ADP-ribosylation of proteins such as NF_kB by poly-ADP-ribose polymerase can trigger the release of apoptosis-inducing factor from mitochondria and therefore effectively mediate apoptosis. Gerth et al.[32] demonstrated that NAD and ADP-ribose, generated from NAD by CD38, an NAD-glycohydrolase, induce the activation of a Ca^{2+} channel through a pathway that involves Ca^{2+} influx in human monocytes. Ca^{2+} ions play a critical role in variety of monocyte functions such as chemotaxis and production of cytokine (TNFα)[33]. Increased intracellular calcium in human monocyte-derived macrophages *in vitro* by loading with the basic calcium phosphate microcrystals was associated with secretion of proinflammatory cytokines (TNFα, IL-1β, and IL-8) capable of activating cultured endothelial cells and promoting capture of flowing leukocytes under shear flow[34].

3. Role of NAMPT in Sepsis

Because of its pleiotropic functions, NAMPT has been implicated in various human diseases[13] including sepsis. Increasing evidence indicates that NAMPT is a risk factor in sepsis. Jia et al. [10] determined the expression of PBEF in neutrophils harvested from 16 critically ill septic patients in an intensive care unit. They found that neutrophils from these patients showed marked expression of PBEF mRNA. PBEF expression was significantly greater in neutrophils from septic patients than in resting neutrophils or LPS-stimulated neutrophils from healthy volunteers. Lee et al. [35] determined the clinical correlates for elevated plasma PBEF upon intensive care unit admission for severe sepsis and the usefulness of NAMPT to predict sepsis mortality. Plasma collected within 24 h of intensive care unit admission was measured for NAMPT concentrations by enzyme-linked immunosorbent assay. They reported that elevated PBEF levels significantly correlated with higher Acute Physiology and Chronic Health Evaluation III scores ($R(2) = 0.08$, $P = .003$). The higher

Acute Physiology and Chronic Health Evaluation III score indicates more severe diseased status. Non-survivors had higher PBEF levels than survivors (2.53 ng/mL; interquartile range [IQR], 1.07-8.16 vs 1.44 ng/mL; IQR, 0.84-2.81; P = .02). They concluded that NAMPT was associated with sepsis mortality mainly due to its association with greater severity of illness on intensive care unit admission. Cekmez et al. [36] found that plasma NAMPT level was significantly higher in septic infants than in healthy ones. There was a positive correlation between NAMPT and other markers (white blood cells, *C-reactive protein*, procalcitonin and IL-6) for sepsis. A cut-off value of 10 ng/mL for NAMPT showed 92% sensitivity and 94% specificity in the diagnosis of sepsis. Thus, the authors proposed that NAMPT could be used as a diagnostic marker similar to *C-reactive protein*, procalcitonin and IL-6 in neonatal sepsis.

In our previous genetic epidemiological study [11], we determined the frequencies of minor alleles, genotypes and haplotypes of two human NAMPT gene promoter SNPs [-1001T>G and -1535C>T (originally labeled as -1543C>T)] in Caucasian septic patients and Caucasian healthy subjects. We found that the frequency of the minor G allele of the SNP -1001T>G was significantly higher (23%) in septic patients than in healthy subjects (12%, p=0.01). Similarly, the frequency of its genotype GT was significantly higher (44%) in septic patients than in healthy subjects (20%, p=0.004). The haplotype-weighted analysis of these two SNPs indicated that a susceptible haplotype GC had a 4.84-fold higher risk of sepsis while a potential protective haplotype TT had a lowest risk of sepsis in a Caucasian patient population among four haplotypes: GC, GT, TC and TT. Our findings were validated and extended in a different patient cohort by Bajwa et al. [12]. They genotyped the NAMPT T-1001G and C-1543T polymorphisms in 375 patients with ARDS, a frequent consequence of sepsis, and 787 patients at risk for developing ARDS. It was found that among the 397 patients with sepsis syndrome, the odds of developing ARDS were significantly increased by presence of T-1001G and among the 561 patients with septic shock, the odds of developing ARDS for patients with C-1543T were significantly decreased. Overall, the NAMPT T-1001G variant allele and related haplotype are associated with increased odds of developing ARDS and increased hazard of intensive care unit mortality among at-risk patients, whereas the C-1543T variant allele and related haplotype are associated with decreased odds of ARDS among patients with septic shock and better outcomes among patients with ARDS. These results support that NAMPT is a genetic risk factor for sepsis.

4. Molecular Mechanisms of NAMPT in Sepsis

Although the role of NAMPT in sepsis is still incompletely understood, accumulating evidence indicates that at least the following molecular mechanisms may in part underlie NAMPT in sepsis (Figure 2).

Augment expressions of other inflammatory cytokines. Sepsis is also known as a systemic inflammatory response syndrome caused by the body's response to infection [1]. Systemic inflammation is a hallmark of sepsis. During the early stage or mild inflammatory response phase of sepsis, a controlled production of proinflammatory cytokines triggers beneficial

inflammatory responses to confine the infection and tissue damage. However, the protracted, excessive production of inflammatory cytokines causes capillary leakage, tissue

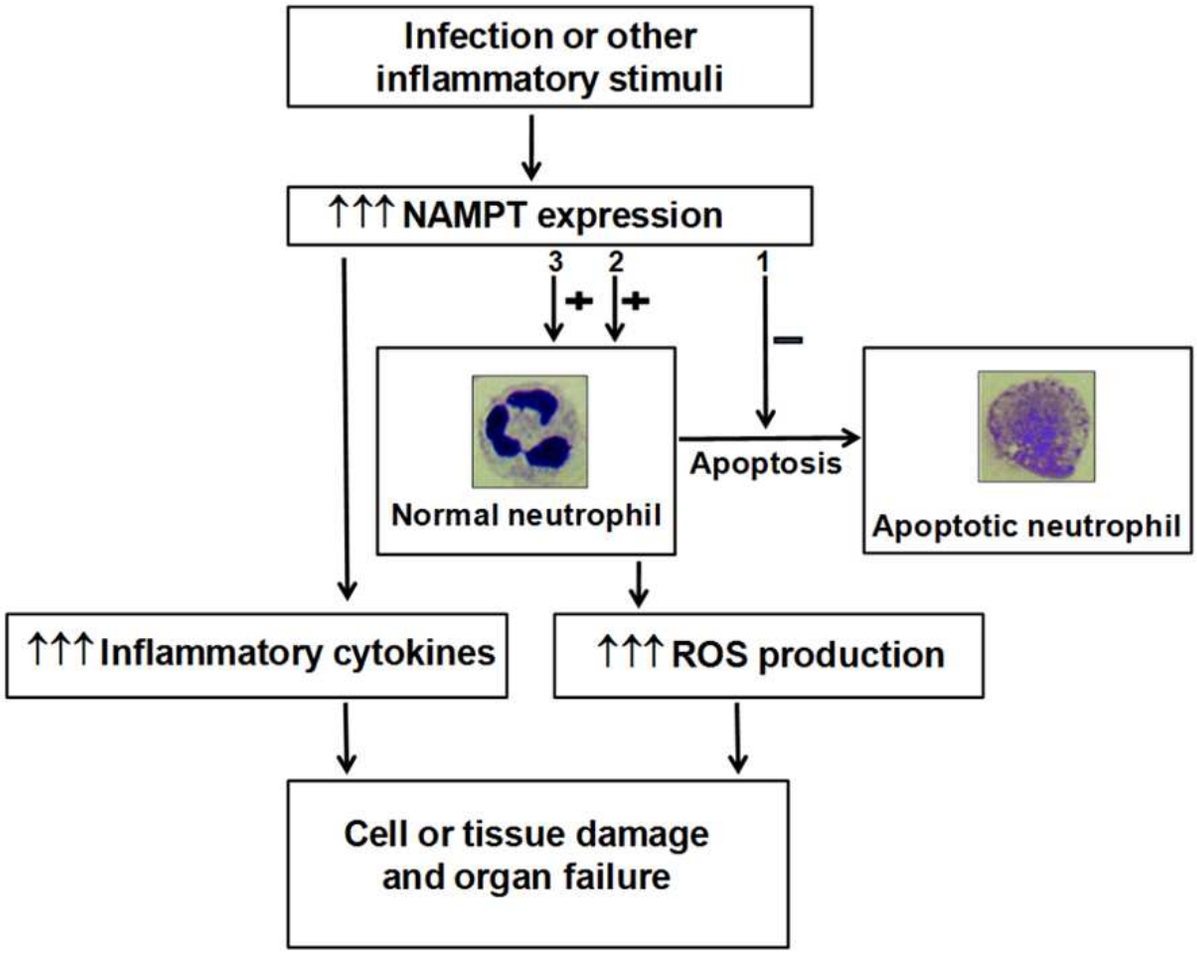

Figure 2. Working mechanisms underlying NAMPT in the pathogenesis of sepsis. During sepsis or prelude to sepsis, bacterial infection or other inflammatory stimuli excessively augment NAMPT expression, which in turn induces an excessive production of other inflammatory cytokines such as TNFα and IL1-β. Dysregulated NAMPT also affects the number and function of neutrophils in one of three ways: 1. inhibiting neutrophills' apoptosis and thus prolonging neutrophil's survival; 2. priming neutrophils for increased ROS generation; 3. acting as a chemotactic factor to neutrophils. Prolonged and increased neutrophils can lead to excessive ROS production. Both excessive expression of inflammatory cytokines and excessive generation of ROS contribute to unwanted side effects such as cell or tissue damage and organ failure in sepsis.

injury, and lethal multiple organ failure in severe sepsis [37]. NAMPT was considered as an inflammatory cytokine [21]. Elevated plasma NAMPT level was associated with sepsis mortality [10, 35]. Elevated NAMPT may augment expressions of other inflammatory cytokines and thus aggravate inflammation, which in part contribute to increased severity and mortality in patients with sepsis.

Besides sepsis, NAMPT expression is up-regulated in a variety of acute and chronic inflammatory diseases including acute lung injury, inflammatory bowel disease, myocardial infarction, and rheumatoid arthritis[13]. It have been demonstrated *in vitro*, that other inflam-

matory stimuli can increase the expression of NAMPT gene. Ognjanovic et al.[17] reported that lipopolysaccharide, IL-1β, TNF α and IL-6 all significantly increased the expression of NAMPT in a 4 h treatment of the amniotic epithelial cell line, WISH cells. The addition of dexamethasone significantly reduced the response to IL-1β and TNFα. They concluded that NAMPT is expressed in the normal fetal membranes and up-regulated when they are infected. NAMPT can also stimulate the expression of other inflammatory cytokines. The rhNAMPT treatment of WISH cells and fetal membrane explants significantly increased IL-6 and IL-8 gene expression[21]. We also found that an overexpression of NAMPT significantly augmented IL-8 secretion and mRNA expression in both human pulmonary carcinoma type II epithelial cell line (A549) and human pulmonary artery endothelial cells. It also significantly augmented IL-1β-mediated cell permeability. The opposite results were obtained with the knockdown of NAMPT expression. NAMPT expression also affected the expression of two other inflammatory cytokines (IL-16 and CCR3 genes)[23, 38]. Our further investigation found that PBEF stimulated expression of IL-8, IL-16, and CCR3 via its non-enzymatic activity. This effect is AP-1-dependent, in part via the p38 MAPK pathway and the JNK pathway[22]. From these results, it can be reasoned that infection in sepsis can induce the expression of NAMPT gene, which in turn stimulate the expression of other inflammatory cytokines, thus aggravating inflammation in sepsis.

Increase number of activated neutrophils. Neutrophils play important roles in host defense against all classes of infectious agents but, paradoxically, they are also involved in the pathology of various inflammatory conditions. Although destruction of infectious agents by neutrophils occurs intracellularly, release of cytotoxic molecules into the extracellular milieu can damage body tissues. Thus, neutrophils is a double-edged sword [39]. Neutrophilia is a prominent feature in sepsis and many lines of evidence link activated neutrophils to the organ injury of sepsis [40]. Jia et al. [10] reported that NAMPT plays a requisite role in the delayed neutrophil apoptosis of clinical and experimental sepsis. They found that transcription of the NAMPT gene is increased in neutrophils from septic patients; prevention of NAMPT translation through the use of an antisense oligonucleotide largely restores the normal kinetics of apoptosis. Moreover, the incubation of quiescent neutrophils from healthy volunteers with recombinant NAMPT results in dose-dependent inhibition of apoptosis, and antisense NAMPT prevents the inhibition of apoptosis that results from exposure to LPS or to a variety of host-derived inflammatory cytokines. They postulated that this prolonged survival of activated neutrophils may be linked to sustained inflammation and the organ injury of sepsis.

The potent antimicrobial activity by neutrophils is effected through proteolytic enzymes and the generation of reactive oxygen species (ROS). ROS released by neutrophils are also implicated in the bystander tissue injury that accompanies an inflammatory response. Malam et al. [41] demonstrated that NAMPT can prime neutrophils for increased ROS generation through the NADPH oxidase. NAMPT promoted membrane translocation of cytosolic NADPH oxidase subunits p40 and p47, but not p67, induced p40 phosphorylation on Thr154, and activated the small GTPase Rac. Priming, translocation, and phosphorylation were dependent on activation of p38 and ERK MAPKs, but not of PI3K. Priming by NAMPT

occurred independently of its NAD-generating capacity because neither nicotinamide mononucleotide nor NAD could recapitulate the effects, and a specific inhibitor of NAMPT, APO-866, could not inhibit priming. This represents another molecular mechanism underlying NAMPT in the pathogenesis of sepsis, in which increased expression of NAMPT contributes to tissue damage by priming neutrophils to produce excessive ROS.

In a different study, Hong et al. [24] demonstrated recombinant human NAMPT as a direct rat neutrophil chemotactic factor in in vitro studies. They also demonstrated a marked increase in bronchoalveolar lavage leukocytes after the intratracheal injection of rhNAMPT into C57BL/6J mice in an acute lung injury model. Organ failure is frequently associated with severe sepsis. Chemoattractant property of NAMPT may also in part account for its role of increasing or activating neutrophils in sepsis.

5. Summary and perspective

Increasing evidence suggest that NAMPT is a risk factor in sepsis. NAMPT is highly up-regulated in sepsis and it has been proposed as a diagnostic marker in neonatal sepsis. It was associated with the severity and mortality of patients with sepsis. Genetic epidemiological studies found that a susceptible haplotype GC in the promoter of human NAMPT gene had a 4.84-fold higher risk of sepsis while a potential protective haplotype TT had a lower risk of sepsis in a Caucasian patient population. Those findings indicate that NAMPT is a potential genetic marker in sepsis. A few molecular mechanisms may underlie role of dysregulated NAMPT in the pathogenesis of sepsis. Infection in sepsis can induce the expression of NAMPT gene, which in turn stimulate the expression of other inflammatory cytokines, thus aggravate inflammation in sepsis. Prolonged survival of activated neutrophils by NAMPT via its inhibition of neutrophil apoptosis may be linked to sustained inflammation and the organ injury during sepsis. NAMPT can act as a chemoattractant to neutrophils. Increased expression of NAMPT in sepsis may also contribute to tissue damage by priming neutrophils to produce excessive ROS.

It remains to be fully elucidated that role of NAMPT in sepsis may be a "double-edged sword". Although accumulated evidence as synopsized in this chapter and summarized in the above paragraph indicates that excessive up-regulation of NAMPT expression in sepsis contributes to excessive inflammation and tissue damage in sepsis, emerging evidence also suggests that a modest increase of NAMPT expression in early phase may be of beneficial value. A recent study by Liu et al. [42] suggested that TLR signaling might increase cellular NAD+ by inducing Nampt expression, which could thereby provide substrate for SIRT1 deacetylase activity. SIRT1 deacetylates RelA/p65 lysine 310 and nucleosomal histone H4 lysine 16 to promote termination of NFκB-dependent transcription, which results in the attenuation of inflammatory response. Thus, Nampt activity promotes endotoxin tolerance.

Therapeutic potential of NAMPT inhibitions to sepsis has not been pursued clinically though several basic and translational studies pointed to the possibility. Jia et al. [10] demonstrated that the NAMPT antisense oligonucleotide prevented the LPS or other inflammatory cytokines' induced neutrophil apoptosis. In neutrophils of patients with

sepsis, addition of PBEF antisense oligonucleotide resulted in a greater than twofold increase in rates of apoptosis. This study indicated that the antisense oligonucleotide to NAMPT could effectively inhibit PBEF expression. Ye et al. [11] reported a successful knockdown of NAMPT expression by more than 70% in human pulmonary vascular endothelial cells using three NAMPT stealth siRNAs in combination or individually. Our group also showed that a NAMPT antibody can block the function of NAMPT in a mouse model [24]. Several chemical inhibitors of NAMPT such as FK866 (also called APO866 or WK175, (E)-N-[4-(1-benzoylpiperidin-4-yl) butyl]-3-(pyridin-3-yl)) and related compounds have been tested to inhibit tumor cell growth [43] and in clinical trials as an anticancer agent [44]. Montecucco et al [45] recently showed that treatment with FK866 reduced myocardial infarct size, neutrophil infiltration and ROS generation within infarcted hearts in vivo in a mouse model of ischemia and reperfusion. It is of interest to explore the therapeutic potential of all these NAMPT inhibitory reagents to sepsis in the clinical setting.

It is anticipated that further elucidation of the role and mechanisms of NAMPT in sepsis will enhance our understanding of molecular pathogenesis underlying NAMPT in sepsis and lead to the development of the NAMPT based strategy and management of sepsis in the future.

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