NAMPT serum levels are selectively elevated in acute infectious disease and in acute relapse of chronic inflammatory diseases in children

Julia Gesing1, Kathrin Scheuermann1,2, Isabel Viola Wagner3, Dennis Löffler4, Daniela Friebe1, Wieland Kiess1,2, Volker Schuster1, Antje Körner1,2*

1 Hospital for Children and Adolescents, University Leipzig, Leipzig, Saxony, Germany, 2 Leipzig University Medical Center (IFB) Adiposity Diseases, Leipzig, Saxony, Germany, 3 Hospital for children and adolescents, University Hospital Cologne, Cologne, North Rhine-Westphalia, Germany, 4 Fraunhofer Institute for Cell Therapy and Immunology Leipzig, Leipzig, Saxony, Germany

* antje.koerner@medizin.uni-leipzig.de

Abstract

Nicotinamide phosphoribosyl transferase (NAMPT) is an inflammatory adipocytokine shown to interact in immune modulation in chronic inflammatory diseases, acute respiratory distress syndrome, sepsis, cancer and obesity in adulthood. It is, however, not clear whether this association reflects a chronic elevation or acute inflammatory response. We analyzed NAMPT concentrations in distinct states of inflammation in 102 children and found consistently significantly increased NAMPT levels in subjects with acute infections. NAMPT concentrations in children with stable chronic inflammatory diseases were not significantly different, whereas in patients with acute relapse of chronic disease NAMPT was significantly higher than in children in remission or healthy controls. In states of low-grade inflammation (children with atopic disease or obesity) we did not detect alterations in NAMPT serum levels. NAMPT correlated positively with inflammatory markers such as CRP. The most predictive factor for NAMPT serum concentrations was leucocyte count and therein the neutrophil count. Furthermore, systemic circulating NAMPT levels were closely associated with NAMPT release from corresponding cultured PBMCs. In conclusion, NAMPT is selectively increased in states of acute but not chronic inflammation in children. The close relationship between systemic circulating NAMPT with leucocyte counts and release indicate that leucocytes most probably are the source of inflammation related NAMPT levels.

Introduction

Nicotinamide phosphoribosyltransferase (NAMPT), also known as Pre-B-cell colony-enhancing factor (PBEF) or visfatin was shown to play a prominent role in cell metabolism, inflammation and immune modulation [1,2]. NAMPT was originally isolated from a cDNA library of human peripheral blood lymphocytes [3] acting as a growth factor for B-cell development.
Later, intracellular NAMPT was found to act as the rate-limiting enzyme in the salvage pathway restoring the cofactor nicotinamide adenine dinucleotide (NAD) in mammals [4]. Recently a knock-out mouse-model showed NAMPT to be an essential gene for survival [5].

In obesity research NAMPT (in this context called visfatin) gained attention as an adipokine [6,7], although its function remains controversial with regard to obesity and glucose metabolism with positive, negative or no associations found [8]. NAMPT variants were associated to childhood obesity in an Indian cohort [9] but not a danish cohort [10]. We have previously shown that the elevated enzymatically active NAMPT levels in obese children are mainly derived from leucocytes and inducible by lipopolysaccharide and hence that NAMPT may serve as a biomarker or even mediator linking obesity, inflammation and insulin resistance [11]. Observations that the highest expression of NAMPT in the human body was found in leucocytes [12], that extracellular NAMPT increases the production of inflammatory cytokines (IL-8, IL6, TNFalpa, IL-1β) [13] and that NAMPT inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis [14] and activates T cells, B cells and monocytes [13] point to a role for NAMPT in inflammation and inflammatory disease. In line with this, NAMPT was shown to be a marker of chronic diseases like inflammatory bowel diseases [15] or rheumatoid arthritis [16] further suggesting that NAMPT is involved in the regulation of inflammation.

There are only few studies focussing on NAMPT in inflammatory states during childhood [17,18]. We have evidence indicating that NAMPT is elevated in childhood obesity and its corresponding low-grade inflammation [12]. In this study we aimed to focus on NAMPT in distinct entities of inflammatory processes during childhood and adolescence. For this, we evaluated NAMPT levels in children and adolescents with acute infections, chronic inflammatory diseases (active and inactive), obesity and atopic diseases in comparison to a healthy control group.

Research design and methods

Patient cohort

We recruited 102 children and adolescents between 0 and 18 years from our inpatient and outpatient units of the University Children’s Hospital Leipzig into this study. Exclusion criteria were oncological, syndromal diseases, and non-inflammatory chronic diseases. Written informed consent was obtained from the legal representatives and children older than 12 years. The study was approved by the ethic committee of the University of Leipzig (Reg. No: 357-10-1312200). Anthropometric data, gender, medical history and medication were documented. We collected serum and EDTA blood samples during clinically indicated venous punctures.

Patients were stratified into four study groups encompassing acute inflammatory states, chronic inflammatory diseases, atopic/allergic manifestations and obese patients (Table 1). The healthy control group consisted of lean and healthy children and adolescents. Obese patients with no other diagnosis were analyzed as their own group. Anthropometric data and the inflammatory profile of each study group are given in Table 2. Mean age was lower in the acute group, whereas naturally anthropometric parameters were higher in the obese group, and also in the atopic group (Table 2 and S1 Table).

Cultivation of peripheral blood mononuclear cells (PBMC)

After collection of EDTA samples leucocytes were separated by centrifugation after lysis of erythrocytes with lysis buffer (8.29 g NH₄Cl; 1 g KHCO₃; 0.0372 g Na-EDTA in 1 l H₂O; pH 7.29). Leucocytes were incubated in RPMI medium containing 0.5% FCS, penicillin and...
Table 1. Clinical diagnosis of probands in the study groups.

| Parameters | Control (n = 15) | Acute (n = 16) | Chronic (n = 36) | Allergic (n = 16) | Obese (n = 19) |
|------------|-----------------|--------------|----------------|-----------------|--------------|
| Acute bronchitis | 3 | 10 | 7 (2) | 9 | 3 |
| Acute pneumonia | 3 | 10 | 7 (3) | 3 | 2 |
| Upper respiratory tract infection | 3 | 10 | 5 (2) | 2 | 1 |
| Acute gastroenteritis | 2 | 10 | 4 | 1 | 1 |
| Kawasaki disease | 1 | 10 | 3 (1) | 1 | 1 |
| Mononucleosis | 1 | 10 | 3 (2) | 1 | 1 |
| Acute Otitis media | 1 | 10 | 2 (2) | 1 | 1 |
| Acute Tonsillitis | 1 | 10 | 2 (1) | 1 | 1 |

*Patients from the chronic group received standard treatment of their underlying disease. 13 patients received steroid and/or immunmodulating medication. 10 Patients received non-steroidal anti-inflammatory medication.

https://doi.org/10.1371/journal.pone.0183027.t001

Table 2. Characterization of the cohort (n = 102).

| Parameters | Control (n = 15) | Acute (n = 16) | Chronic (n = 36) | Allergic (n = 16) | Obese (n = 19) |
|------------|-----------------|--------------|----------------|-----------------|--------------|
| Anthropometric | | | | | |
| Male / Female | 10/5 | 13/3 | 11/25 | 11/5 | 10/9 |
| Age (years) | 11.93 ±5.35 | 0.92–17.9 | 5.27 ±4.81 | 0.37–16.6 | 10.8 ±4.21 | 0.51–16.6 | 11.08 ±2.7 | 5.63–5.08 | 12.97 ±3.03 | 5.8–17.93 |
| Pubertal stage | 1.56 ±0.73 | 1–3 | 1 ±0 | 1 | 1.29 ±0.46 | 1–2 | 1.4 ±0.74 | 1–3 | 1.72 ±0.36 | 1–3 |
| Height SDS_MLS | -1.09 ±1.46 | -4.3 | 0.18 ±1.15 | -4.45 | -0.23 ±1.1 | -5.23 | 0.11 ±1.61 | -6.14 | 0.67 ±1.39 | -5.39 |
| BMI (kg/m²) | 18.6 ±2.57 | 14.15–22.1 | 17.61 ±3.3 | 13.16–23.98 | 18.05 ±3.41 | 12.65–28.69 | 24.73 ±8.19 | 13.08–41.5 | 31.43 ±6.04 | 24.37–6.05 |
| BMI SDS_MLS | -0.47±0.66 | -3.32–0.98 | 0.57±1.26 | -0.97–2.78 | 0.008 ±1.17 | -2.04–2.22 | 1.42±1.69 | -2.8–3.48 | 2.6±0.77 | 1.41–4.6 |
| Lean (BMI < 1.22 SDS_MLS) | 15 | 13 | 31 | 5 | 0 |

Inflammatory

| Parameters | Control (n = 15) | Acute (n = 16) | Chronic (n = 36) | Allergic (n = 16) | Obese (n = 19) |
|------------|-----------------|--------------|----------------|-----------------|--------------|
| CRP (mg/l) | 1.63 ±2.49 | 0.15–6.58 | 21.2 ±49.9 | 0.38–200.13 | 1.57 ±2.11 | 0.15–7.48 | N/A | N/A |
| ESR 1h (mm) | 7.2 ±3.55 | 2–13 | 42 ±5.94 | 37–50 | 15.14 ±9.55 | 2–37 | 16.86 ±13.13 | 7–45 | 18.77 ±19.85 | 2–70 |
| Leucocyte count (/nl) | 6.42 ±1.92 | 3.8–10.6 | 9.52 ±2.79 | 5.1–15.6 | 8.47 ±4.15 | 3.5–21.1 | 5.78 ±1.23 | 4.3–8.6 | 6 ±1.4 | 4.4–9.6 |
| Lymphocytes (/nl) | 2.6 ±1.42 | 1.51–6.69 | 3.01±1.72 | 1.08–6.55 | 2.87±2.57 | 0.62–15.81 | 2.03±0.49 | 1.3–3.06 | 2.19±0.78 | 1.12–4.11 |
| Monocytes (/nl) | 0.54 ±0.17 | 0.26–0.88 | 1.06±0.67 | 0.32–2.69 | 0.66±0.36 | 0.16–1.83 | 0.55±0.17 | 0.31–0.91 | 0.49±0.11 | 0.21–0.64 |
| Neutrophil Granulocytes (/nl) | 2.91 ±1.05 | 0.96–4.69 | 5.13 ±3.47 | 0.63–12.8 | 4.73 ±2.97 | 0.16–1.83 | 2.97 ±0.84 | 2.02–4.63 | 3.12 ±1.15 | 1.87–6.52 |
| Basophil Granulocytes (/nl) | 0.04 ±0.03 | 0.01–0.12 | 0.09 ±0.07 | 0.02–0.06 | 0.03±0.04 | 0–0.21 | 0.02±0.01 | 0.01–0.04 | 0.02±0.01 | 0.01–0.05 |
| Eosinophil Granulocytes (/nl) | 0.32 ±0.43 | 0.06–1.7 | 0.15 ±0.21 | 0–0.73 | 0.17±0.14 | 0–0.63 | 0.2 ±0.09 | 0.06–0.34 | 0.17±0.17 | 0.05–0.64 |

BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SDS_MLS, standard deviation score; Pubertal stage (1 = prepubertal; 2 = pubertal, 3 = postpubertal). Significant p-values (p<0.05) are indicated in bold. Non-normally distributed data was log-transformed before analysis.

https://doi.org/10.1371/journal.pone.0183027.t002
streptomycin at 37°C for one hour before harvesting of cells and supernatant fractions. Cells could be harvested and supernatants obtained in 80% of controls, 50% of patients with acute infections, 64% of patients with chronic disease, 100% of patients with allergies and 95% of obese subjects.

Quantification of NAMPT in serum samples and supernatants

NAMPT concentrations were measured in serum samples and supernatant fractions by ELISA following the manufacturer’s protocol (Adipogen, Seoul, South Korea). Assay quality variables including sensitivity and specificity have been validated as published before [12].

Analyses of inflammatory markers

Inflammatory markers were assessed by a certified laboratory (Institute of Laboratory medicine, clinical chemistry and molecular diagnostics Leipzig, Germany) applying routine diagnostic procedures. The C-reactive protein (CRP) was measured with the CRPL3 immunoturbidimetric assay (Roche Diagnostics GmbH) on Roche/Hitachi cobas systems. The hemogram was assessed with automated blood count using laser flow cytometry, electrical impedance and cyanide-free sodium lauryl sulphate methods on a Sysmex XE2100.

Statistical analyses

Logarithmic transformation of non-normally distributed data was performed before analysis. For comparison of quantitative traits between groups, one-way ANOVA was applied. Correlation analyses were performed using Pearson correlation analysis or partial correlation analysis with adjustment for height SDS_{LMS} (standard deviation score using the LMS values by Kroemer-Hausschild [19]) and neutrophil granulocyte count. For multiple regression analyses the stepwise forward model was used. For all tests, the significance level was set at 0.05. Statistical analyses were performed using the software package Statistica 7.1 (StatSoft, Tulsa, OK, USA) and GraphPad Prism5.

Results

NAMPT serum concentrations are increased in acute states of inflammation

To evaluate whether NAMPT serum concentrations are associated with acute or chronic inflammation, atopic status, or obesity, we measured NAMPT in serum samples in our cohort. We found highest NAMPT levels in the acute group compared to the healthy controls and all other study groups (Fig 1A). No difference was found in NAMPT serum concentrations between patients with chronic inflammatory diseases, allergic manifestations or obesity compared to the healthy lean controls.

Considering that disease activity may differ in patients with chronic inflammatory diseases we compared NAMPT serum concentrations of patients with active chronic disease or relapse of clinical symptoms to patients in remission and healthy controls. We found significantly higher NAMPT serum concentrations in the subgroup with symptomatic chronic disease compared to patients in remission (Fig 1B).

Hence, overall NAMPT is increased in acute but not in chronic states of inflammation or infection.
NAMPT serum concentrations are associated with markers of inflammation

Considering our results on selectively increased NAMPT levels in acute inflammation, we next analyzed the association of NAMPT with common inflammatory markers. NAMPT serum concentrations correlated positively with CRP and the erythrocyte sedimentation rate (ESR) (Fig 2A and 2B). We did, however, find highest correlation of NAMPT serum levels with the leucocyte count (Fig 2C). In a general linear model including age, patient study group and the inflammatory parameters ESR, CRP and leucocyte count, the leucocyte count solely predicted (log) NAMPT serum levels ($\beta = 0.679$, $p = 0.002$), hence independent from the pathologic origin of inflammation.

Differential analyses on leucocyte subspecies revealed the highest correlation of NAMPT with neutrophil granulocyte count (Fig 2D) and also to some degree with monocyte count ($r = 0.24$, $p = 0.022$), whereas there was no relationship with lymphocytes, basophil or eosinophil granulocyte counts.

Hence, the inflammation associated increase in NAMPT serum levels was most closely related to neutrophil granulocyte counts.

Systemic NAMPT levels are related to NAMPT release from corresponding PBMCs

To assess whether leucocytes directly contribute to inflammatory associated NAMPT increase, we evaluated NAMPT release into supernatants of peripheral blood mononuclear cells (PBMCs) of our patients. We found no significant difference between the patient groups (Fig 3A). But NAMPT release from PBMCs correlated closely with NAMPT serum levels (Fig 3B), particularly with the neutrophil granulocyte subset (Fig 3C).
Hence, the NAMPT production and release by leucocytes appears to underline the association with inflammatory markers in states of acute inflammation.

**Discussion**

In this study we show that circulating levels of NAMPT are selectively increased in children and adolescents with acute infections and symptomatic chronic inflammatory conditions compared to healthy controls and also compared to patients with asymptomatic chronic inflammatory diseases, allergic manifestations or obesity. We further show that the increased NAMPT serum levels correlated with inflammatory parameters and most closely with blood leukocyte counts, particularly neutrophils, and indeed release of NAMPT protein from PBMC was related to systemic serum NAMPT levels.
Only few studies analyzed NAMPT in the context of inflammatory processes in childhood [17,18]. We had previously shown, that mainly mono- and granulocytes secrete circulating NAMPT and that mildly elevated leucocytes in obesity may contribute to the phenomenon of slightly increased NAMPT levels in low-grade inflammation in obesity [12]. We, therefore, were interested whether NAMPT may serve as an inflammatory parameter in other types of inflammation. Here, we found that the increase in NAMPT with inflammation is selective for acute inflammation as in infections or in acute relapse of chronic inflammation, also in comparison to other, more subtle types such as atopic disease or chronic inflammation. We suppose the increased NAMPT serum concentration in acute inflammatory response and relapse of chronic inflammation is due to its release from neutrophil granulocytes. Naturally, there is leucocytosis with or without relative neutrophilia in acute inflammation or monocytosis in chronic inflammation.

Fig 3. NAMPT release from PBMCs. Comparison of NAMPT release between patient groups of distinct inflammatory conditions and controls (A). Boxes are interquartile range, whiskers are minimum to maximum. Statistical significance was assessed by ANOVA and Tukey HSD test. Correlation between log NAMPT serum concentrations and corresponding NAMPT release from PBMCs of the same patient (B) and Correlation between NAMPT release from PBMCs with blood neutrophil counts (C).

https://doi.org/10.1371/journal.pone.0183027.g003
One may assume that the release of extracellular NAMPT is triggered by inflammation markers in inflammatory conditions. If this was the case we could assume that activated granulocytes release more NAMPT than resting granulocytes. We therefore evaluated NAMPT release into supernatants of cultured PBMCs of our patients, which did not differ significantly between different inflammatory states and the controls. Limitations were the small number of PBMC cultivation and the heterogeneous groups. Still we see a positive correlation of NAMPT release to the number of neutrophils in the blood count and also to NAMPT serum concentrations.

Comparing all patients with chronic inflammatory diseases to the control group did not show significant differences in NAMPT serum levels. Only, when we compared the subgroup of patients with symptomatic chronic disease to patients in remission or the control group, significantly higher NAMPT serum concentrations, comparable to those in patients with acute infections were detected. This is partly in line with reports where NAMPT was found to be a marker of chronic inflammation [20] in adults and correlated positively to disease activity in inflammatory bowel disease [21], rheumatoid arthritis [22], Graves’ disease with association with autoantibody titer [23] or also in local inflammatory disease of periodontitis [24]. Furthermore, microbial and inflammatory signals such as IL-1β were shown to locally enhance NAMPT synthesis [25]. It is, however, not clear whether this association reflects a chronic elevation in persisting inflammation or is limited to acute inflammatory response. We extend these findings by showing that in our pediatric cohort particularly in chronic active disease, but not as strong in chronic stable disease, NAMPT serum levels were elevated. We speculate that NAMPT could serve as a marker for disease activity of chronic inflammatory disease and severity of inflammation status. This is in line with one previous report where NAMPT was increased in acute pneumonia and associated with severity and leucocyte count [26]. Also in neonatal sepsis NAMPT was found to be significantly elevated [18]. NAMPT was a predictor of mortality in sepsis and pneumonia [26,27].

The majority of patients with chronic diseases were under treatment with non-steroidal anti-inflammatory or immune-modulating medication. We cannot exclude that NAMPT levels were altered by this treatment. Still, we detected the highest NAMPT level in the chronic group (8.3 ng/ml) in a patient with Crohn’s disease under immune-modulating therapy. We can assume that no matter if there is an effect of the medication to NAMPT levels, higher levels indicate higher disease activity. This could be of value in the treatment of children with chronic inflammatory diseases.

The mechanism by which NAMPT interacts with the immune response in not fully clear yet. NAMPT catalyzes the rate-limiting step in the salvage pathway for NAD(+) biosynthesis, and thereby regulates the deacetylase activity of sirtuins [8]. This NAMPT-NAD(+) SIRT axis has been postulated in articular chondrocytes to be involved in cartilage destruction in osteoarthritis [28]. NAMPT was further reported to induce lung NFκB transcriptional activities and inflammatory injury via direct ligation of Toll-like receptor 4 (TLR4) [29]. A deeper insight into these mechanisms may also provide new therapeutic strategies in inflammatory disease. Even beyond the mere clinical association with inflammatory disease such as juvenile idiopathic arthritis, NAMPT was found to inhibit the pharmacological activity of methotrexate and was suggested as a predictive biomarker of response, as well as a potential therapeutic target [30]. NAMPT inhibition with FK866 has anti-inflammatory activity in different models of immune disorders through lowering the production of neutrophil chemoattractants [1]. NAMPT blockade also had beneficial effects in an acute lung injury model and may modify the cancer microenvironment through their anti-inflammatory properties [31]. In animal models symptoms of inflammatory arthritis and autoimmune encephalomyelitis improved...
after treatment with NAMPT inhibitors [32,33]. From those reports, NAMPT inhibition is likely to hold potential for the treatment of inflammation-related disorders.

Low-grade inflammation is present in obesity and atopic diseases and an increase of NAMPT serum concentration in obese children and adolescents has been shown previously [8,34,35]. We, therefore, expected increased NAMPT levels for these groups. However, we did not find altered NAMPT concentrations in obese children, neither did we detect differences in NAMPT levels in patients with atopic diseases compared to healthy controls. We suppose that differences between the groups are smaller than we could detect in this analysis due to the limited number of participants in our study.

Regarding anthropometric data no relevant factors influencing NAMPT serum concentrations could be detected. In correlation analysis age was found to be negatively associated with NAMPT levels, which did, however, not withstand adjustment to height SDS and neutrophil count. In our cohort patients with acute infectious diseases were younger than the remaining cohort (because acute infections leading to hospitalization are more common in infants than in older children), which may have biased the univariate analysis. Our previous studies in healthy children did not show a correlation of NAMPT with age [11]. Looking into literature no significant relationship between NAMPT and age, gender, pubertal stage, height or circumferences of waist and hip had been evident in multivariate analysis [34]. Hence, no strong evidence for any independent anthropometric factor on NAMPT serum levels could be detected.

Conclusion

In conclusion we report that NAMPT is a selective marker for acute and active chronic inflammation in children. NAMPT may hence also serve as an indicator for disease activity in chronic inflammatory diseases. The close relationship of systemic circulating NAMPT with leucocyte counts and release indicate that leucocytes, particularly neutrophils, are the source of inflammation associated NAMPT levels.

Supporting information

S1 Table. Multiple regression analysis in the cohort. (DOCX)

Acknowledgments

We thank the pediatric endocrinology and immunology teams and colleagues for their assistance in the collection of blood samples. This work was supported by the German Research Foundation (DFG) for the Clinical Research Center “Obesity Mechanisms” CRC1052/1 C05 and by the LIFE (Leipzig Research Center for Civilization Diseases, Universität Leipzig), funded by the European Union, by the European Regional Development Fund (ERFD) by means of the Free State of Saxony within the framework of the excellence initiative, and by the Federal Ministry of Education and Research (BMBF), Germany, Integrated Research and Treatment Centre (IFB) Adiposity Diseases FKZ: 01EO1001.

Author Contributions

Conceptualization: Julia Gesing, Isabel Viola Wagner, Antje Körner.

Data curation: Julia Gesing, Kathrin Scheuermann, Isabel Viola Wagner, Volker Schuster.

Formal analysis: Julia Gesing, Isabel Viola Wagner.

Funding acquisition: Antje Körner.
Investigation: Julia Gesing, Kathrin Scheuermann, Isabel Viola Wagner, Volker Schuster.
Methodology: Kathrin Scheuermann, Isabel Viola Wagner, Dennis Löfler, Daniela Friebe.
Resources: Antje Körner.
Supervision: Dennis Löfler, Wieland Kiess, Volker Schuster, Antje Körner.
Validation: Dennis Löfler, Daniela Friebe, Wieland Kiess, Antje Körner.
Writing – original draft: Julia Gesing, Antje Körner.
Writing – review & editing: Julia Gesing, Kathrin Scheuermann, Isabel Viola Wagner, Dennis Löfler, Wieland Kiess, Volker Schuster, Antje Körner.

References
1. Montecucco F, Cea M, Cagnetta A, Damonte P, Nahimana A, Ballestro A, et al. Nicotinamide phosphoribosyltransferase as a target in inflammation-related disorders. Curr Top Med Chem. 2013; 13: 2930–2938. PMID: 24171767
2. Garten A, Petzold S, Schuster S, Körner A, Kratzsch J, Kiess W. Namp t and its potential role in inflammation and type 2 diabetes. Handb. Exp. Pharmacol. 2011; 147–164. https://doi.org/10.1007/978-3-642-17214-4_7 PMID: 21484571
3. Samal B, Sun Y, Stearns G, Xie C, Suggs S, McNiece I. Cloning and characterization of the cDNA encoding a novel human pre-B-cell colony-enhancing factor. Mol Cell Biol. 1994; 14(2): 1431–1437. PMID: 8269818
4. Rongvaux A, Shea RJ, Mulks MH, Gigot D, Urbain J, Leo O, et al. Pre-B-cell colony-enhancing factor, whose expression is up-regulated in activated lymphocytes, is a nicotinamide phosphoribosyltransferase, a cytosolic enzyme involved in NAD biosynthesis. Eur. J Immunol. 2002; 32(11): 3225–3234. https://doi.org/10.1002/1521-4141(200211)32:11<3225::AID-IMMU3225>3.0.CO;2-L PMID: 12555668
5. Zhang LQ, Van Haandel L, Xiong M, Huang P, Heruth DP, Bi C, et al. Metabolic and molecular insights into an essential role of nicotinamide phosphoribosyltransferase. Cell Death Dis. 2017; 23; 8(3):e2705. https://doi.org/10.1038/cddis.2017.132 PMID: 28333140
6. Kralisch S, Klein J, Lossner U, Blüher M, Paschke R, Stumvoll M, et al. Hormonal regulation of the novel adipocytokine visfatin in 3T3-L1 adipocytes. J Endocrinol. 2005; 185(3):R1–8. https://doi.org/10.1677/joe.1.06211 PMID: 15930160
7. Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science. 2005. 307: 426–430. https://doi.org/10.1126/science.1097243 PMID: 15604363
8. Garten A, Petzold S, Körner A, Imai S, Kiess W. Namp t: linking NAD biology, metabolism and cancer. Trends Endocrinol Metab. 2009; 20: 130–138. https://doi.org/10.1016/j.tem.2008.10.004 PMID: 19109034
9. Tabassum R, Mahendran Y, Dwivedi OP, Chauhan G, Ghosh S, Marwaha RK, et al. Common variants of IL6, LEPR, and PBEF1 are associated with obesity in Indian children. Diabetes. 2012; 61(3):626–631. https://doi.org/10.2337/db11-1501 PMID: 22282719
10. Hollensted M, Ahuwalia TS, Have CT, Grarup N, Fonvig CE, Nielsen TR, et al. Common variants in LEPR, IL6, and NAMPT do not associate with risk of juvenile and childhood obesity in Danes: a case-control study. BMC Med Genet. 2015; 11:16:105. https://doi.org/10.1186/s12881-015-0253-3
11. Friebe D, Neef M, Kratzsch J, Erbs S, Dittrich K, Garten A, et al. Leucocytes are a major source of circulating nicotinamide phosphoribosyltransferase (NAMPT)/pre-B cell colony (PBEF)/visfatin linking obesity and inflammation in humans. Diabetologia. 2011; 54: 1200–1211. https://doi.org/10.1007/s00125-010-2042-z PMID: 21298414
12. Körner A, Garten A, Blüher M, Tauscher R, Kratzsch J, Kiess W. Molecular characteristics of serum visfatin and differential detection by immunoassays. J Clin Endocrinol Metab. 2007; 92(12): 4783–4791. https://doi.org/10.1210/jc.2007-1304 PMID: 17878256
13. Moschen AR, Kaser A, Enrich B, Mosheimer B, Theurl M, Niederegger H, et al. Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. J Immunol. 2007;1; 178(3): 1748–1758.
14. Jia SH, Li Y, Parodo J, Kapus A, Fan L, Rotstein OD, et al. Pre-B cell colony-enhancing factor inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis. J Clin Invest. 2004; 113(9): 1318–1327. https://doi.org/10.1172/JCI19930 PMID: 15124023
15. Dogan S, Guven K, Celikbilek M, Deniz K, Saraymen B, Gursoy S. Serum Visfatin Levels in Ulcerative Colitis. J Clin Lab Anal. 2016; 30(5):552–556. https://doi.org/10.1002/jcla.21901 PMID: 26668098

16. Meier FM, Frommer KW, Peters MA, Brentano F, Lefevre S, Schroder D, et al. Visfatin/pre-B-cell colony-enhancing factor (PBEF), a proinflammatory and cell motility-changing factor in rheumatoid arthritis. J Biol Chem. 2012; 287: 28378–28385. https://doi.org/10.1074/jbc.M111.312884 PMID: 22765982

17. Gao ZY, Li XY, Bhandari V, Li LD, Lan D. Pre-B-cell colony-enhancing factor is markedly elevated in childhood hemophagocytic lymphohistiocytosis. Genet Mol Res. 2015;18; 14(2):5287–5295. https://doi.org/10.4238/2015.May.18.21 PMID: 26125724

18. Cekmez F, Canpolat FE, Cetinkaya M, Aydinoz S, Aydemir G, Karademir F, et al. Diagnostic value of resistin and visfatin, in comparison with C-reactive protein, procalcitonin and interleukin-6 in neonatal sepsis. Eur Cytokine Netw. 2011;6; 22(2):113–117. https://doi.org/10.1684/ecn.2011.0283 PMID: 21636351

19. Kromeyer-Hausschild K, Wabitsch M, Kunze D, Geller F, Geiß HC, Hesse V, et al. Perzentile für den Body-mass-Index für das Kindes- und Jugendalter unter Heranziehung verschiedener deutscher Stichproben. Monatschr Kinderheilkd. 2001; 149: 807–818

20. Tilg H and Moschen AR. Adipokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev.Immunol. 2006; 6: 772–783. https://doi.org/10.1038/nri1937 PMID: 16998510

21. Valentini L, Wirth EK, Schweitzer U, Hengstermann S, Schaper L, Koernicke T, et al. Circulating adipokines and the protective effects of hyperinsulinemia in inflammatory bowel disease. Nutrition. 2009; 25 (2): 172–181. https://doi.org/10.1016/j.nut.2008.07.020 PMID: 18849144

22. Brentano F, Schorr O, Ospelt C, Stanczyk J, Gay RE, Gay S, et al. Pre-B cell colony-enhancing factor/visfatin, a new marker of inflammation in rheumatoid arthritis with proinflammatory and matrix-degrading activities. Arthritis Rheum. 2007; 56(9): 2829–2839. https://doi.org/10.1002/art.22833 PMID: 17763446

23. Sawicka-Gutaj N, Budny B, Zybek-Kocik A, Sowinski J, Ziemnicka K, Waligorska-Stachura J, et al. Nicotinamide phosphoribosyltransferase enzymatic activity identifies a new inflammatory pathway linked to NAD. PLoS One. 2008;21; 3(5):e2267. https://doi.org/10.1371/journal.pone.0002267 PMID: 18493620

24. Schuster S, Penke M, Gorski T, Gebhardt R, Weiss TS, Kiess W, et al. Pharmacologic inhibition of nicotinamide phosphoribosyltransferase Attenuates Methotrexate Response in Juvenile Idiopathic Arthritis and In Vitro. Clin Transl Sci. 2016; 9(3):149–157. https://doi.org/10.1111/cts.12399 PMID: 27166432

25. Funk RS, Singh R, Pramanam L, Gigliotti N, Islam S, Heruth DP, et al. Nicotinamide Phosphoribosyltransferase Attenuates Methotrexate Response in Juvenile Idiopathic Arthritis and In Vitro. Clin Transl Sci. 2016; 9(3):149–157. https://doi.org/10.1111/cts.12399 PMID: 27166432

26. Damanaki A, Nokhbehsaim M, Eick S, Gotz W, Winter J, Wahl G, et al. Regulation of NAMPT in human gingival fibroblasts and biopsies. Mediators Inflamm. 2014; 912821. https://doi.org/10.1155/2014/912821 PMID: 24707118

27. Broekema LM, Roos MM, Schipper BO, van der Velden DA, Reuser AJ. Regulation of MMP-1 and CCL2 by NAMPT in PDL cells. Mediators Inflamm. 2013; 2013:437123. https://doi.org/10.1155/2013/437123 PMID: 24058270

28. Oh H, Kwak JS, Yang S, Gong MK, Kim JH, Rhee J, et al. Reciprocal regulation by hypoxia-inducible factor-2alpha and the NAMPT-NAD(+)--SIRT axis in articular chondrocytes is involved in osteoarthritis. Osteoarthrits Cartilage. 2015; 23(12):2288–2296. https://doi.org/10.1016/j.joca.2015.07.009 PMID: 26209889

29. Camp SM, Ceco E, Evenoski CL, Danilov SM, Zhou T, Chiang ET, et al. Unique Toll-Like Receptor 4 Activation by NAMPT/PBEF Induces NFkappaB Signaling and Inflammatory Lung Injury. Sci Rep. 2015; 5:13135. https://doi.org/10.1038/srep13135 PMID: 26272519

30. Funk RS, Singh R, Pramanam L, Gigliotti N, Islam S, Heruth DP, et al. Nicotinamide Phosphoribosyltransferase Attenuates Methotrexate Response in Juvenile Idiopathic Arthritis and In Vitro. Clin Transl Sci. 2016; 9(3):149–157. https://doi.org/10.1111/cts.12399 PMID: 27166432

31. Schuster S, Penke M, Gorski T, Gebhardt R, Weiss TS, Kiess W, et al. Fk866-induced NAMPT inhibition activates AMPK and downregulates mTOR signaling in hepatocarcinoma cells. Biochem Biophys Res Commun. 2015; 458(2): 334–340. https://doi.org/10.1016/j.bbrc.2015.01.111 PMID: 25665579

32. Busso N, Karababa M, Nobile M, Rolaz A, Van Gool F, Galli M et al. Pharmacological inhibition of nicotinamide phosphoribosyltransferase visfatin enzymatic activity identifies a new inflammatory pathway linked to NAD. PLoS One. 2008;21; 3(5):e2267. https://doi.org/10.1371/journal.pone.0002267 PMID: 18493620

33. Bruzzzone S, Fruscione F, Morando S, Ferrando T, Poggi A, Garuti A et al. Catastrophic NAD+ depletion in activated T lymphocytes through NAMPT inhibition reduces demyelinization and disability in EAE. PLoS One. 2009;19; 4(11):e7887. https://doi.org/10.1371/journal.pone.0007897 PMID: 19936064
34. Haider DG, Holzer G, Schaller G, Weghuber D, Widhalm K, Wagner O et al. The adipokine visfatin is markedly elevated in obese children. J Pediatr Gastroenterol Nutr. 2006; 43(4): 548–549. https://doi.org/10.1097/01.mpg.0000235749.50820.b3 PMID: 17033537

35. Martos-Morenó GA, Sackmann-Sala L, Barrios V, Berrymann DE, Okada S, Argente J, et al. Proteomic analysis allows for early detection of potential markers of metabolic impairment in very young obese children. Int J Pediatr Endocrinol. 2014; 2014(1):9. https://doi.org/10.1186/1687-9856-2014-9 PMID: 24949022