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The Linkage Between Coenzyme A Metabolism and Inflammation: Roles of Pantetheinase

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Abstract. Pantetheinase is an enzyme hydrolyzing pantetheine, an intermediate of the coenzyme A degradation pathway. Pantetheinase has long been considered as the enzyme that recycles pantothenic acid (vitamin B_5) generated during coenzyme A breakdown. Genetic analyses showed that mammals have multiple genes known as vanin family genes. Recent studies using mice lacking the vanin-1 gene (pantetheinase gene) suggest that pantetheinase is actively involved in the progression of inflammatory reactions by generating cysteamine. Additional studies using human leukocytes demonstrate that human neutrophils have abundant pantetheinase proteins on the surface and inside the cells. The second pantetheinase protein, GPI-80/VNN2, is suggested to work as a modulator of the function of Mac-1 (CD11b/CD18), an adhesion molecule important to neutrophil functions. This review delineates the characteristics of the pantetheinase/vanin gene family and how they affect inflammation.

Keywords: inflammation, pantetheinase, cysteamine, neutrophil, oxidative stress

1. Introduction

Inflammation is the protective response by the host organism that ultimately rids injured tissues of both the cause and the consequences of injury (1). The cardinal signs of acute inflammation are dolor, calor, and rubor, which if not resolved in a timely manner lead to chronic inflammation, scarring, and eventual loss of the tissue and/or organ function (1). It is now evident that beyond established inflammatory diseases such as psoriasis and arthritis, chronic inflammation governs the symptoms and pathogeneses of other prevalent diseases including cardiovascular and cerebrovascular disease, cancer, obesity, and Alzheimer's disease.

Coenzyme A (CoA) has long been recognized as an essential cofactor of biochemical reactions such as carboxylic acid metabolism, including short- and long-chain fatty acids in various organisms (2). CoA is generated from pantothenic acid (vitamin B_5) through a series of five synthetic reactions. CoA catabolism occurs as the reverse of the biosynthetic pathway except that 4′-phosphopantetheine is converted to pantetheinase followed by conversion to pantothenic acid by the pantetheinase enzyme (Fig. 1) (2). Recent research on CoA metabolic enzymes has led to the discovery of uniquely non-metabolic roles for both enzymes and their metabolites. Pantetheinase and its product cysteamine appear to be inflammatory enhancers.

"Pantetheinase" activity was first identified in the crude horse kidney extracts by its ability to cleave pantethine, an oxidized form of pantetheine, into pantothenic acid and cysteamine (3). Pantetheinase, as a purified enzyme was later isolated from horse kidneys (4). Protein sequence comparisons of the pantetheinase to other proteins established that it is a homolog to the protein vanin-1 in mice (5). In mice, three genes related to pantetheinase are recorded in international databases (5 – 10). In this review, we discuss recent studies about pantetheinase and its roles in inflammatory diseases. Pantetheinase function has been primarily investigated in both vanin-1–deficient mice and human leukocytes. We also discuss the possibility of cysteamine's involvement in inflammation and potential novel anti-inflammatory drugs that modify pantetheinase activity.

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Invited article

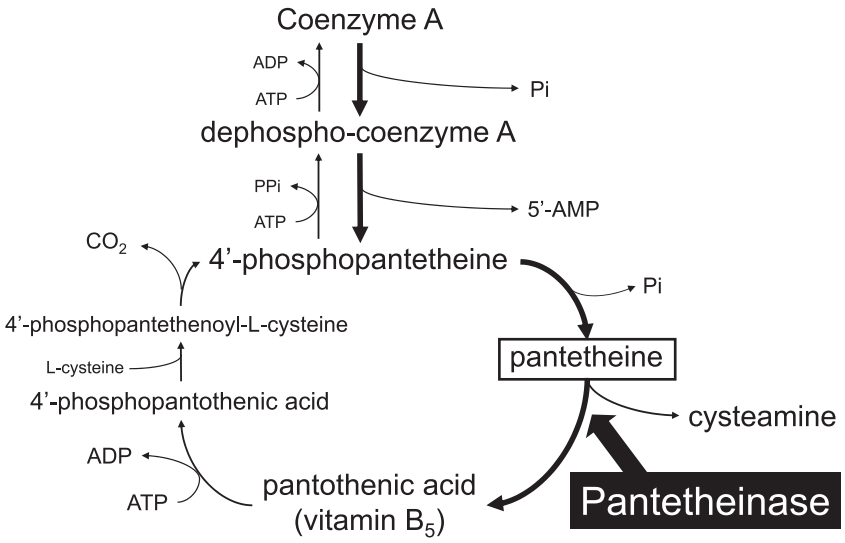

Fig. 1. Metabolic and synthetic pathway of coenzyme A (CoA). Schematic of metabolic pathway of CoA is indicated with downward arrows. CoA is dephosphorylated at the 3′ position of ribose to form dephosphoCoA. DephosphoCoA is then degraded to 4′-phosphopantetheine and 5′-AMP. Dephosphorylation of 4′-phosphopantetheine forms pantetheine. In the final step in the metabolic pathway, pantetheine is degraded to pantothenic acid (vitamin B_5) and cysteamine (β-mercaptoethylamine) by pantetheinase. Since pantothenic acid generated during the CoA degradation is recycled for another biosynthesis of CoA (indicated by upward arrows), the step of hydrolysis of pantetheine by pantetheinase is important for the "salvage pathway" of CoA biosynthesis. ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; PPi; pyrophosphate; Pi, phosphate.

Table 1. Pantetheinase gene family in human and mouse

Human (located at locus 6q23-24)		
Gene name	length (kbp)	Tissue expression profile
VNN1, Pantetheinase	32.4	spleen, small intestine, peripheral blood leukocyte, liver
VNN2, GPI-80	14.0	neutrophils, monocytes, colon, spleen, placenta, lung
VNN3	12.0	spleen, peripheral blood leukocyte, liver
Mouse (located at the locus 10A2B1)		
Gene name	length (kbp)	Tissue expression profile
Vanin-1, Pantetheinase	10.6	kidney, small intestine, liver, testis, heart
Vanin-3	18.4	spleen, peripheral blood leukocyte, liver, kidney, thymus, heart

Summary of the comparison of the five pantetheinase genes focusing on gene names, locus in human and mouse, gene length (kilo base pairs), and the tissues in which the five genes are mainly expressed.

2. Pantetheinase gene family

2.1. Pantetheinase/vanin-1/VNN1

Vanin-1 was first identified as the molecule recognized by a monoclonal antibody to murine thymic stromal cell line (6), which regulates adhesion of the thymocytes and thymus homing. The vanin-1 genes have been identified in mouse, human, rat, chicken, and 16 other organisms according to the NCBI database. Regarding mice and humans, the pantetheinase/vanin gene family are clustered on chromosome 10A2B1 of mice (7, 10), and the human analog (VNN1) is on chromosome 6q23-24 (7, 8) (Table 1). Although the murine vanin-1 was first cloned from a thymic stromal cell line, the expression of vanin-1 mRNA is also found in the small intestine, kidney, liver, and other immunological tissues (11) (Table 1). Mouse vanin-1 is induced by the activation of two antioxidant response elements in epithelial cells (12). On the other hand, the pantetheinase protein was purified from porcine kidney by tracing the enzymatic activity that hydrolyzes pantetheine into pantothenic acid and cysteamine. Mouse pantetheinase/vanin-1 is produced as a glycosylphosphatidyl inositol (GPI)-anchored protein and is located on the plasma membrane of epithelial cells. In addition, the pantetheinase protein was shown to be expressed in the human kidney. The mouse vanin-1 functions are best documented, since vanin-1–deficient mice have been generated and analyzed (see below).

2.2. GPI-80/VNN2

Humans have two pantetheinase-related genes, GPI-80/VNN2 and VNN3. Galland et al. (7) identified two human cDNAs homologous to mouse vanin-1 during the screening of human kidney, liver, and placental cDNA libraries; the two genes are named VNN1 and VNN2 after the mouse vanin-1 gene. Suzuki et al. (9) identified a protein recognized by the monoclonal antibody, 3H9, which modulated adhesion and transmigration of activated human neutrophils; this protein was named

GPI-80 (80-kDa protein with GPI-anchor). It was later determined that Suzuki and Galland had independently identified the same gene, GPI-80/VNN2. Queries of the mouse genome have not uncovered a homologue of GPI-80/VNN2, suggesting that the gene was divided from the common orthologue of vanin-1/VNN1 and GPI-80/VNN2 during evolution from rodents to primates. The amino acid sequences of the potential amidohydrolase active center are conserved between human VNN1 (pantetheinase) and GPI-80/VNN2. GPI-80/VNN2 was determined to have pantetheinase enzymatic activity (10), but the activity is weaker than that of VNN1. Finally, both pantetheinase/vanin-1/VNN1 and GPI-80/VNN2 are biosynthesized as GPI-anchored protein. GPI-80/VNN2 mRNAs are expressed in leukocytes, colon, spleen, placenta, and lung. The expression of GPI-80/VNN-2 increases in neutrophil progenitors during both differentiation and maturation (13).

2.3. Vanin-3/VNN3

Vanin-3 in mouse and VNN3 in humans have somewhat different features compared to the two proteins described above. Mouse vanin-3 is a soluble protein without a GPI-anchor (10). Therefore, the protein may not be anchored on the plasma membrane or the other cellular membranes. Vanin-3 expression is found in normal mouse tissue such as spleen, peripheral blood leukocyte, liver, kidney, thymus, and heart. Vanin-3 expression is induced by oxidative stress, which is involved in the antioxidant response as well as mouse vanin-1 gene (12). While the mouse vanin-3 has pantetheinase activity (10), the putative human vanin-3 homologue (VNN3) seems to encode a truncated protein (14). This suggests that human VNN3 is either encoding a protein other than pantetheinase or a pseudogene.

It has been shown that several alternative splice variants are generated from the human GPI-80/VNN2 and VNN3 genes (14). Although their specific functional differences remain to be elucidated, products derived from these alternative splice variants may have some biological activities other than pantetheinase enzyme. Human VNN3 mRNA is reported to be expressed in the lung, liver, and peripheral blood cells (10, 15). Jansen et al. (15) also demonstrated that the human VNN3 mRNA is detected in inflamed skin keratinocytes that are induced by inflammatory cytokines, and VNN3 is elevated in psoriatic skin lesions. Metallothionein-deficient neonatal mice have augmented expression of vanin-3 (16). Given that mouse vanin-3 has comparable pantetheinase activity to vanin-1 (10) and produces cysteamine, vanin-3 might compensate for the role of metallothionein as the acute phase stress response.

3. Roles of pantetheinase in the regulation of inflammation in vivo

3.1. Vanin-1 deficient mice

Among the three proteins belonging to the pantetheinase gene family, pantetheinase/vanin-1/VNN1 has been best characterized in physiological and pathophysiological conditions by using vanin-1–deficient mice (summarized in Table 2). Vanin-1–deficient mice lack detectable cysteamine (11), one of the metabolites of pantetheine, suggesting that vanin-1 is the major enzyme for pantetheine hydrolyzation in mice. Vanin-1–deficient mice exhibit resistance to apoptotic oxidative tissue injury caused by γ-irradiation or by the administration of paraquat (12). They also show an attenuated inflammatory bowel reaction in response to the administration of non-steroidal anti-inflammatory drugs (17) or 2,4,6-trinitrobenzene sulfonic acid (18) and to *Schistosoma manosoni* infection (17). Administration of peroxisome proliferator-activated receptor (PPAR) γ antagonist inhibited the alleviation of the inflammation (18), suggesting that vanin-1/pantetheinase acts as either a direct or indirect antagonist to the anti-inflammatory factor PPARγ. This is consistent with the finding that exposure of human mononuclear cells to oxidative stress inducers elicited dramatic up-regulation of human VNN1 and down-regulation of PPARγ (19). Vanin-1 deficiency affects chondrogenesis in bone marrow stromal cells (20) and granuloma formation against *Coxiella burnetii*, a bacterium that causes Q fever, due to alteration of macrophage function (21). The above results strongly suggest that pantetheinase is involved in promoting inflammation during an infection.

3.2. Cysteamine — a key player in inflammation and host defense

As shown above, mice lacking pantetheinase exhibit weaker inflammatory response compared to wild type, which could be due to a loss of pantetheine hydrolyzation and subsequent decrease in both cysteamine and pantothenic acid. Extensive investigations using vanin-1/pantetheinase–deficient mice show that cysteamine is the more reasonable candidate for promoting an inflammatory response. Vanin-1–deficient mice lack free cysteamine in tissues and exhibit elevated stores of the reduced form of glutathione (GSH) in multiple tissues instead (12). Cysteamine breaks the disulfide bonds yielding mixed disulfides and inactivate proteins (Fig. 2, hatched arrow pointing left). Cysteamine also directly inhibits γ-glutamylcysteine synthase (Fig. 2), the rate-limiting enzyme involved in the synthesis of GSH. As suspected, vanin-1–deficient mice have increased γ-glutamylcysteine synthase activity, resulting in increased tissue stores of

Table 2. Phenotype of vanin-1–deficient mice

Phenotype	Reference
Fertile, born normally, growing and developing normally under normal conditions	(11)
Unable to metabolize pantetheine in liver and kidney, very low tissue cysteamine levels	(11)
Increase in	
the level of reduced form of glutathione in tissues	(12, 17)
γ-glutamylcysteine synthetase activity	(12)
Delayed death caused by	
administration of lethal dose of paraquat	(12)
γ-irradiation	(12)
2,4,6-trinitrobenezene sulfonic acid	(18)
Schistosoma mansoni infection	(17)
Suppression of	
intestinal inflammation caused by administration of indomethacin and *Schistosoma mansoni* infection	(17)
unusual bone marrow stromal cells and chondrogenic transdifferentiation and calcification of aortic smooth muscle cells derived from *ank*/*ank* mice	(20)
incidence of colitis-associated colon cancer	(24)
granuloma formation in liver and spleen after the infection with *Coxiella burnetii*	(21)
the incidence of diabetes in NOD mice	(23)
Decrease in selenium-independent glutathione peroxidase activity and the GSTA3 protein level	(22)
Failure to induce inflammatory mediators including cytokines in response to stress	(12, 17, 18, 21, 23, 24)
Induction of peroxisome proliferator activator receptor-γ	(18)

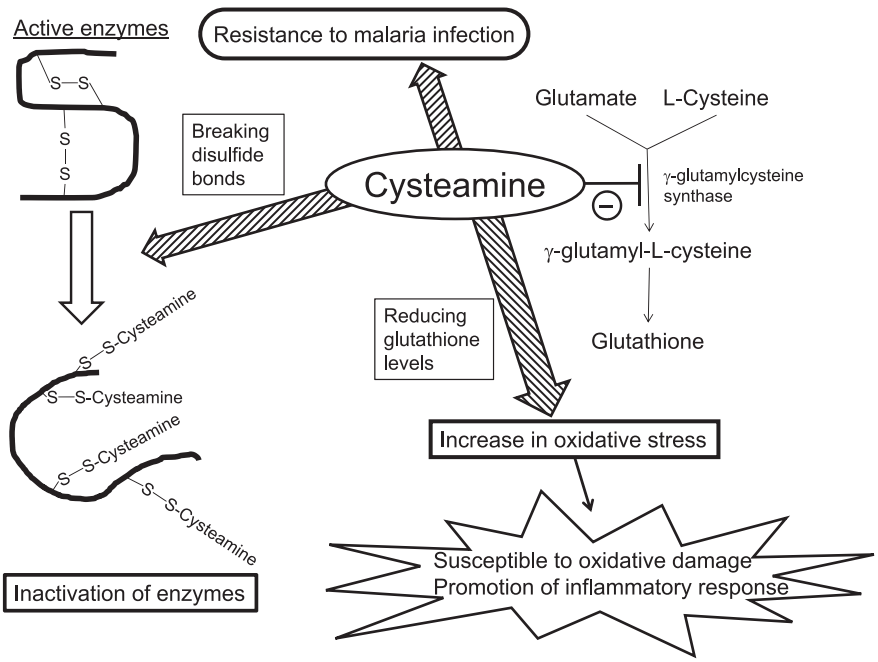

Fig. 2. The roles of cysteamine in inflammation and host defense. Cysteamine has a free sulfhydryl group, which can cleave sulfhydryl bonds inside the proteins, leading to destruction of the structure of functional proteins such as enzymes, receptors, bioactive peptides, and so on (hatched arrows pointing left). Cysteamine also inhibits γ-glutamylcysteine synthase, a rate limiting enzyme, to produce glutathione, rendering cells and tissues susceptible to oxidative damage presumably generated during inflammation (hatched arrows pointing downward). On the other hand, cysteamine has a protective feature against malaria infection, although the precise mechanisms remain to be elucidated (hatched arrows pointing upward).

GSH (12, 17), suggesting that vanin-1/pantetheinase regulates the glutathione-dependent response to oxidative stress. GSH is a redox stress regulator that is the primary form of reduced intracellular thiol. Therefore, increased cysteamine levels in tissue means increased oxidative stress, rendering the tissues susceptible to damage by reactive oxygen species generated during inflammation (Fig. 2, hatched arrow pointing downward). In addition, vanin-1–deficient mice show a decreasing level of selenium-independent glutathione peroxidase

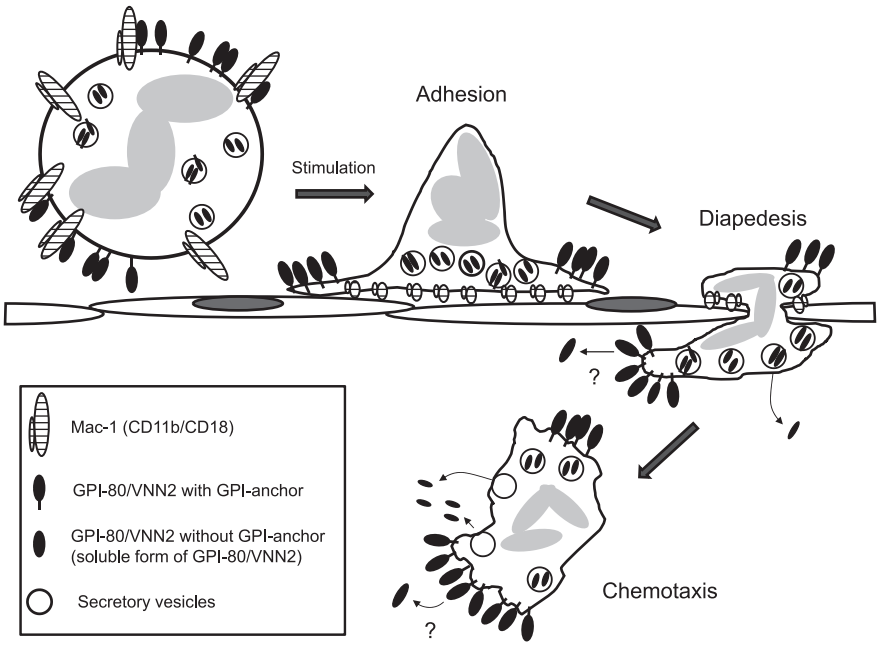

Fig. 3. Schematics of the localization of GPI-80/VNN2 molecules in human neutrophils during extravasation. Neutrophils have GPI-anchored GPI-80/VNN2 associated with Mac-1 on the cellular surface, whereas the soluble form of GPI-80/VNN2 (i.e., GPI-80/VNN2 without GPI-anchor) is stored in secretory vesicles. Once activated by stimulators, neutrophils adhere to endothelial cells via Mac-1 and migrate into the interstitial space. During adhesion to endothelial cells, GPI-80/VNN2 may dissociate from Mac-1, and some of the GPI-anchored GPI-80/VNN2 may move to the pseudopodia of the neutrophil. Adherence via Mac-1 conversely stimulates neutrophils (outside-in signals), resulting in the release of GPI-80/VNN2 from internal vesicles. The majority of the soluble GPI-80/VNN2 released from neutrophils is derived from the intracellular stores. It has not yet been confirmed whether GPI-anchored GPI-80/VNN2 on the cell surface and inside the secretory vesicle is cleaved by specific enzymes followed by the release from the cellular surface. Black ellipses show GPI-80/VNN2, and striped ellipses show dimers of Mac-1 (CD11b/CD18 dimer).

activity and the GSTA3 protein (22). In humans, GSH/GSSG levels are inversely correlated to VNN1 gene expression levels in chronic idiopathic thrombocytopenic purpura patients. These results suggest that pantetheinase production of cysteamine is an important regulating factor in cellular redox status.

Based upon these observations, vanin-1–deficeint mice were administered cysteamine or cystamine, an oxidized form of cysteamine, to determine if cysteamine alone can recover the inflammatory response. Results show that the vanin-1–deficeint mice supplemented with cysteamine had a similar inflammatory response to control wild-type mice (12, 17, 18, 21, 23, 24). This suggests that cysteamine is a key molecule that induces inflammatory response and is a possible route for medical intervention. It has also been demonstrated that the mouse *Char9* locus that encodes pantetheinase/vanin-1 is a marker for malarial susceptibility (25). The A/J strain mice, which are not able to produce pantetheinase protein and cysteamine, are susceptible to malaria infection. Administration of cysteamine to these mice partially corrects susceptibility to malaria (25). Therefore, cysteamine is expected to be a new medicine to treat malaria infection resistant to currently used medicines (26) (Fig. 2, hatched arrow pointing upward).

3.3. Roles of GPI-80/VNN2 on neutrophil functions

Neutrophils are a host's first cellular immune response to injury by exiting from the bloodstream into the injured tissues (1). Neutrophil extravasation is essential for subsequent inflammation and the immune response. Extravasation can be divided into at least three steps: rolling, firm adhesion, and transendothelial migration. β_2-Integrins including Mac-1, a dimer of CD11b and CD18, have pivotal roles on the last two steps. GPI-80/VNN-2 associates with the important adhesion molecule Mac-1 (27, 28) and is thought to modulate Mac-1 functionality because the antibody 3H9 differentially modulates the adhesion to fibrinogen, a counter-ligand to Mac-1, and transmigration of neutrophils (9). After neutrophils attach to the vessel wall, GPI-80/VNN2 may migrate to pseudopodia of the human neutrophil. Bound GPI-80/VNN-2 concentrates on the neutrophil surface closest to attractive chemotactic factors, such as

formyl-methyonyl-leucyl phenylalanine (fMLP) (29) (Fig. 3). Lipid rafts are important for physical and functional association between GPI-80/VNN2 and Mac-1 (30). In human neutrophils, GPI-80/VNN2 is mostly found in plasma membrane (9, 31), but secretory vesicles are the other considerable reservoir of intracellular GPI-80/VNN2 (31). The GPI-80/VNN-2 stored in secretory vesicles is considered to be a soluble form (Fig. 3). Interestingly, there are two structurally divergent forms of GPI-80/VNN2 depending upon the reactivity to a monoclonal antibody, 4D4, that recognizes a certain carbohydrate moiety of GPI-80/VNN2: one is present on the cell surface and the second form is sequestered in vesicles within the cells (32). The form recognized by 4D4 may regulate Mac-1–dependent neutrophil adhesion and may subsequently be converted to a 4D4-unrecognized form upon neutrophil activation. Stimulation with fMLP (33) and TNF-α (34) induces the release of the soluble GPI-80/VNN2. It is presumed that the soluble form is released from secretory vesicles rather than GPI-anchored protein on the cell surface because activation hardly changes the expression levels of GPI-80/VNN2 on the cell surface (34). The release of soluble GPI-80/VNN2 requires adherence of ligand to Mac-1 such as fibrinogen and iC3b (34) (Fig. 3), suggesting that signaling through subsequent activation of β_2-integrin by stimulants such as TNF-α and fMLP is important for the release of GPI-80/VNN2 (34). Pyrrolidine dithiocarbamate and *N*-acetylcysteine, both of which modulate the intracellular redox level directly, affect the release of GPI-80/VNN2, implying a relationship between the change in intracellular redox levels and the release of GPI-80/VNN2 (34). Since the soluble GPI-80/VNN2 is detected in synovial fluids of rheumatoid arthritis patients (33), and serum derived from coronary sinus of the patients with isolated atherosclerotic coronary artery disease (35), GPI-80/VNN2 could be an indicator of inflammatory severity, especially from neutrophil activation.

4. Pantetheinase family genes and proteins as indicators of human diseases

Many researchers report that increased expression of pantetheinase family members could be a useful diagnostic indicator for chronic inflammatory diseases. Since pantetheinase protein was originally purified from horse kidney and vanin-1/VNN-1 mRNA is abundant in kidney tissue, one can speculate that detection of pantetheinase levels in urea and/or changes in mRNA expression in kidney tissues would reflect renal tissue damage. One report by Fugmann et al. (36) showed that concentrations of VNN1 distinguished diabetic patients with macroalbuminuria from those with normal albuminuria. Another report by Hosohata et al. (37) showed that urinary pantetheinase is derived from damaged tubular kidney cells. It can thus be used as an earlier and equally sensitive marker for cisplatin- and gentamicin-induced acute kidney injury damage, compared with current detection methods including urinary Kim-1 and neutrophil gelatinase-associated lipocalin. This correlation was also shown to occur between human VNN1 expression in whole blood cells and chronic pediatric immune thrombocytopenia (19). In this case, VNN1 overexpression is correlated with PPARγ down-regulation (19). Soluble GPI-80/VNN2 protein is suggested to be an indicator of acute phase neutrophil activation in arthritis (33) and myocardial infarction (35). It is reported that human VNN1 and VNN3 expression increases in psoriatic skin lesions compared with normal individuals (15) although the clinical significance of the enhanced VNN3 expression remains to be elucidated.

5. Conclusion

In addition to CoA metabolism, the pantetheinase family genes and the metabolite cysteamine are also major players in the inflammatory and oxidative response. In human neutrophils, it is suggested that one of the pantetheinase family molecules directly and/or indirectly modulates the function of cellular adhesion molecule. However, the precise details of their individual and collective roles in inflammation are unknown. In addition, the regulation of the pantetheinase genes remains to be fully elucidated. Targeting pantetheinase enzymatic activity by specific inhibitors may result in the generation of a new class of anti-inflammatory drugs. As a recent example of this, Jansen et al. (38) reports that a synthetic pantetheine analogue, RR6, strongly inhibited recombinant human VNN-1 at 0.54 μM IC_{50}. RR6 inhibits human, fetal bovine, and rat serum pantetheinase, but not human serum biotinidase, another amidohydrolase family enzyme with different substrate specificity. This compound will be a new tool to clarify the role of pantetheinase in progression of human chronic inflammatory diseases and kidney diseases. Modulation of pantetheinase activity could be an additional target in the treatment of chronic inflammatory diseases.

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