Ananyl aminopeptidase as marker in pathological disorders

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Abstract: Alanylaminopeptidase is one of most known metallo-containing proteases that selectively hydrolyzes an amino acid residue from the N-terminus of proteins and peptides. Its activity is indicated in mammalian tissues and organs, in plants and in single cell organisms, what is attributed to its importance for the proper functioning of prokaryotic and eukaryotic cells. Elevated and abnormal concentration of this enzyme is correlated with many pathological disorders such as cancer, leukemia and malaria. In these cases, the activity of alanylaminopeptidase creates a potential to develop new generations of diagnostic systems where APN will be used as a marker. This paper presents a short review of the pathological disorders that APN is the biomarker for and whose diagnosis it could facilitate.

1. Introduction

The enzyme alanylaminopeptidase (E.C. 3.4.11.2, aminopeptidase N, APN, also known as CD13), belonging to the family M1 and clan MA, is a zinc-dependent exopeptidase that degrades proteins and peptides with N-terminal neutral amino acids (Hooper, 1994; Rawlings and Bartrett, 1999). APN exists in two forms, namely the transmembrane and the soluble. Soluble APN, does not contain transmembrane part, is detectable in plasma, serum and urine Luan and Xu (2007). The mechanism of its release from the membrane type is still unknown. The membrane aminopeptidase N (APN/CD13) is a dimer combined by noncovalent bond. Every unit consists of 967 amino acids with a short N-terminal cytoplasmic domain, a single transmembrane part and a large cellular ectodomain containing the active site with one Zn$^{2+}$ ion which is required for the catalytic process (Luan and Xu, 2007; Bavois and Dauzonne, 2006). The domain structure of the APN contains seven domains, namely the domain I to domain VII (Hans et al., 2000).

Aminopeptidase N is a widespread enzyme that exists in many mammalian tissues and organs, in plants and single cell organisms. It is expressed on several types of
cells including highly expressed on the brush border membranes of the kidney, mucosal cells of the small intestine and in the liver. APN is also distributed in the brain, the spinal cord and other nerve tissues and cells. Moreover, APN presents on endothelial cells and synaptic membranes and is also found to exist on astrocytes and pericytes (Hans et al., 2000; Luan and Xu, 2007).

In mammals APN has a variety of functions, including roles in inflammatory and immunological responses, signal transduction, antigen processing, neuropeptide processing and cytokine degradation (Mina-Osorio, 2008; Zhang and Xu, 2008; Wickström et al., 2011). An abnormal concentration of this protease is observed in pathological disorders, including cancer.

APN expressed by single cell organisms is mostly responsible for proteolysis and nutrition delivery what is directly responsible for the clinical symptoms of diseases caused by infection with these organisms (Skinner-Adams et al., 2010; Supuran et al., 2002).

APN has extensive substrate specificity. The physiological role played by APN is based on the removal of the amino acid from the unsubstituted N-terminal of various biologically active peptides such as enkephalins, angiotensins, neurokinins and cytokines. Recently, Drag has published a series of papers about the substrate specificities of alanylaminopeptidases from different organisms, investigated using fluorogenic method (Drag et al., 2010).

Alanine aminopeptidase is a multifunctional enzyme that performs diverse functions in mammals and other organisms. This paper reviews the most interesting pathological disorders in which APN is overexpressed.

2. APN as a marker in pathological disorders

APN is ubiquitous in the body, which demonstrates its essential role in physiological processes. It is also overexpressed in certain types of pathological disorders.

It is well known that APN is expressed at high levels in tumor cells, thereby mediating the angiogenesis, tumor invasion and metastasis, cell-cell contact and proliferation (Wickström et al., 2011; Zhang and Xu, 2008).

On the surface of the endepidermis of a tumor, APN is the receptor of tumornathing peptide motif, NGR peptidase (asparagine–glycine–arginine, Asn–Gly–Arg), which is capable of homing selectively to the tumor vasculature \textit{in vivo} (Fabio et al., 2003). In line with this, APN is involved in the antigen processing and is expressed in many kinds of immune cells such as T cells, B cells and macrophages (Luan and Xu, 2007).

Human aminopeptidase N (APN) is used as a routine marker for myelomonocytic cells in hematopoietic malignant disorders (Alfalah et al., 2006). APN can be useful for differentiate normal and neoplastic liver tissue during hepatocellular carcinoma (Röcken et al., 2005).

APN has been shown to have a significant relationship with angiogenesis which is indispensable for supplying nutrients and oxygen to tumors cells. Angiogenesis is a physiological process where new blood vessels are grown from pre-existing vasculature. Spread of tumor cells into other tissues is a critical step in tumor progression (Sato, 2004). Apart from the pro-angiogenic function in the development of malignant tumorogenesis, APN is involved in the extracellular matrix degradation. This
promotes the growth and metastasis of the primary tumor (Xu and Li, 2005; Luan and Xu, 2007).

The knowledge that APN is associated with increased malignancy of cancers is common. Here, it is shown chosen less popular correlation of APN with pathological disorders.

One of the disorders that APN is over-expressed is rheumatoid arthritis. It was demonstrated that alanylaminopeptidase might be a useful marker for activity of the inflamed joint in rheumatoid arthritis and consequent for diagnosis of the disease. What is more APN might play a role in the mechanism of lymphocyte involvement in this disorder (Shimizu et al., 2002).

The urinary activity of alanylaminopeptidase is known to elevate markedly in the initial phase of clinical acute renal failure (ARF) (Suzuki, 1991; Barragán et al., 1985). The presence of APN in the urinary can also signify chronic alcohol abuse. The activity of a urinary APN connected with alcohol-related kidney impairment might complement the existing set of markers of chronic alcohol abuse, which have been based mainly on the assessment of hepatotoxicity (Taracha et al., 2004). The urinary alanine aminopeptidase is also reliable biomarkers of nephrotoxicity and represent early indicator of tubular damage (Holdt et al., 2008).

Investigation of the APN activity in urinary for diagnostic work and toxicological studies is easy. The automated assay developed in 2008 (Holdt et al., 2008) isa user-friendly analytical tool to determine urinary APN activity in a medium- to high-throughput laboratory.

It was indicated that APN activity might serve as a marker for collagen vascular diseases (CVD). The researchers suggested that this protease might play a role in the mechanism of tissue inflammation in CVD. A greater understanding of the regulation of APN production and action might lead to new insights for the control and treatment of CVD (Dan et al., 2003).

APN is also involved in the processing of enkephalins – endogenous opioid peptides, which are extensively present in the central nervous system and constitute the most significant analgesia medium of the CNS. In this way, APN next to NEP (neutral endopeptidase), located on human neutrophils, plays a role in several modalities of pain. The research showed that APN activity in the group of patients with chronic pain was significantly increased in comparison with that activity in a group of healthy volunteers (Luan and Xu, 2007; Abe et al., 1998).

3. Conclusion

Alanylaminopeptidase is a critical enzyme for significant biological processes, of both physiological and pathological character. Many studies have revealed that APN is related with various kinds of cancers for example colon cancer, prostate cancer, lung cancer, liver cancer and leukemia. Unexpectedly abnormal concentration and activity of APN is also associated with diseases such as rheumatoid arthritis, collagen vascular diseases, chronic pain, nephrotoxicity, renal failure, chronic alcohol abuse and many others. This short review presents several of these disorders and shows that alanylaminopeptidase could be a useful tool to diagnose many dangerous disease, all the easier as APN activity detections have been investigated.
Presented work shows the correlations of APN activity with selected pathological disorders and opportunity to make good use of this enzyme as a biomarker of many disorders.

References


