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Review

Autotaxin, Pruritus and Primary Biliary Cholangitis (PBC)

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ABSTRACT

Autotaxin (ATX) is a 125-kD type II ectonucleotide pyrophosphatase/phosphodiesterase (ENPP2 or NPP2) originally discovered as an unknown "autocrine motility factor" in human melanoma cells. In addition to its pyrophosphatase/phosphodiesterase activities ATX has lysophospholipase D (lysoPLD) activity, catalyzing the conversion of lysophosphatidylcholine (LPC) into lysophosphatidic acid (LPA). ATX is the only ENPP family member with lysoPLD activity and it produces most of the LPA in circulation. In support of this, ATX heterozygous mice have 50% of normal LPA plasma levels. The ATX-LPA signaling axis plays an important role in both normal physiology and disease pathogenesis and recently has been linked to pruritus in chronic cholestatic liver diseases, including primary biliary cholangitis (PBC). Several lines of evidence have suggested that a circulating puritogen is responsible, but the identification of the molecule has yet to be definitively identified. In contrast, plasma ATX activity is strongly associated with pruritus in PBC, suggesting a targetable molecule for treatment. We review herein the biochemistry of ATX and the rationale for its role in pruritus.

Contents

1. Introduction

Pruritus is a major issue in a number of autoimmune diseases, including, in particular, primary biliary cholangitis (PBC) [1–5]. Autotaxin (ATX) is a 125-kD type II ectonucleotide pyrophosphatase/phosphodiesterase (ENPP2 or NPP2) originally discovered as an unknown "autocrine motility factor" in human melanoma cells [6,7]. In addition to its pyrophosphatase/phosphodiesterase activities ATX has lysophospholipase D (lysoPLD) activity, catalyzing the conversion of lysophosphatidylcholine (LPC) into lysophosphatidic acid (LPA). ATX is the only ENPP family member with lysoPLD activity and it produces most of the LPA in circulation. In support of this, ATX heterozygous mice have 50% of normal LPA plasma levels [8].

ATX is a secreted glycoprotein comprising a N-terminal signal peptide sequence with a furin cleavage site. ATX contains four domains, including two N-terminal somatomedin B-like (SMB) domains, a central catalytic phosphodiesterase (PDE) domain and a C-terminal nuclease-like (NUC) domain [6]. The crystal structures of mouse [6] and rat [9] ATX indicate loop regions located on both sides of the catalytic

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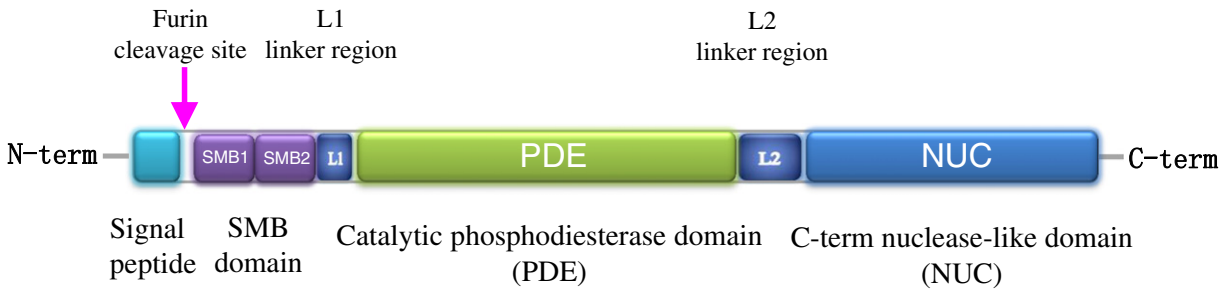

Fig. 1. Domain structure of ATX.

domain, which determine the binding specificity. A short loop (L1 linker region) connects the SMB and PDE domains and a long "lasso loop" (L2 linker region), wrapped around the NUC domain, connects the PDE and NUC domains (Fig. 1) [6]. It has been suggested that sequences in these domains together constitute a lysophospholipid (LPL)-binding pocket with preference for unsaturated acyl chains. When LPLs occupy this site nucleotides are unable to bind and since there are high quantities of LPC in circulation the major role of ATX *in vivo* is as a lysoPLD.

The ATX gene has a complex structure, and is located on chromosome 15 in mouse and on chromosome 8q24.1 in the human. There are five alternatively-spliced isoforms of ATX that are catalytically active (ATX α- δ) and expressed in different tissues. ATX β and ATX δ are the major and stable isoforms [8]. The ATX gene is conserved through evolution and the genes are nearly identical in humans and mice [9].

2. Pathways of LPA production

LPA (1- or 2-acyl-sn-glycerol 3-phosphate) is a lipid made up of phosphate, glycerol, and fatty acid moiety [10–13]. LPA and its major precursor LPC comprise molecular species that vary in length and degree of saturation of their fatty acid chain, which is esterified at the sn-1 (or, less common, sn-2) position of the glycerol backbone. LPA, through activation of at least 6 specific G protein coupled receptors (GPCRs), participates in many cellular processes including cellular proliferation, blood vessel formation, lymphocyte entry into secondary lymphoid organs, prevention of apoptosis, cell migration, cytokine and chemokine secretion, platelet aggregation, smooth muscle contraction, cytoskeletal reorganization and neurite retraction [14,15] (Fig. 2).

LPA is produced both extracellularly and intracellularly. Significant amounts of LPA have been detected extracellularly in biological fluids, including serum, plasma, follicular fluid, saliva, and seminal fluid

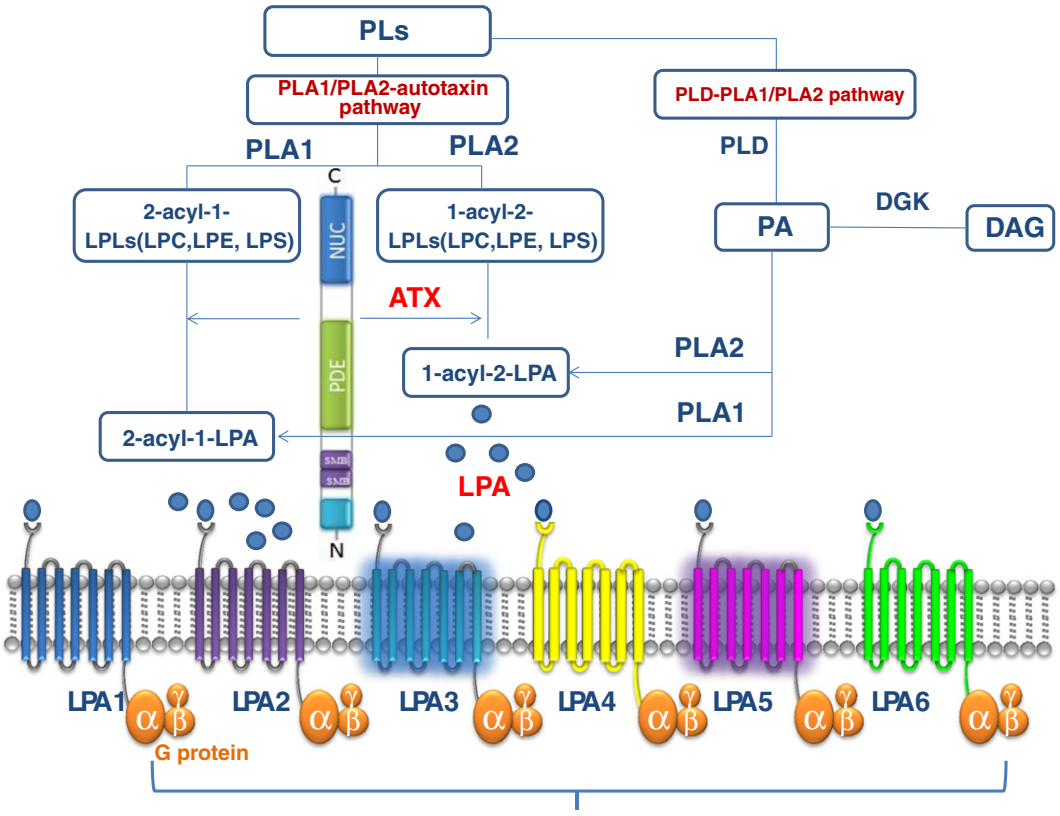

Fig. 2. Pathways of LPA production and LPA-ATX signaling axis. PLs phospholipids, PLA phospholipase A, PA phosphatidic acid, LPA Lysophosphatidic acid,PLD phospholipase D, DAG diacylglycerol, DGK diacylglycerol kinase. Two pathways of LPA production: A.PLA1/PLA2-autotaxin pathway;B.PLD-PLA1/PLA2 pathway.