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Review

Autotaxin, a secreted lysophospholipase D, as a promising therapeutic target in chronic inflammation and cancer

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ABSTRACT

Autotaxin (ATX) is a member of the nucleotide pyrophosphatase/phosphodiesterase family of ectoenzymes that hydrolyzes phosphodiester bonds of various nucleotides. It possesses lysophospholipase D activity, catalyzing the hydrolysis of lysophosphatidylcholine into lysophosphatidic acid (LPA), and it is considered the major LPA-producing enzyme in the circulation. LPA is a bioactive phospholipid with diverse functions in almost every mammalian cell type, which exerts its action through binding to specific G protein-coupled receptors and stimulates various cellular functions, including migration, proliferation and survival. As a consequence, both ATX and LPA have attracted the interest of researchers, in an effort to understand their roles in physiology and pathophysiology. The present review article aims to summarize the existing knowledge as to the implications of ATX in chronic inflammatory diseases and cancer and to highlight the low molecular weight compounds, which have been developed as leads for the discovery of novel medicines to treat inflammatory diseases and cancer.

Contents

Abbreviations: ABTS, 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid); AML, acute myeloid leukemia; Ap_nA, diadenosine polyphosphates; ATP, adenosine-5′-triphosphate; ATX, autotaxin; BALF, bronchoalveolar lavage fluid; bis-pNPP, bis(p-nitrophenyl) phosphate; BLM, bleomycin; CAM, chorioallantoic membrane; CNS, central nervous system; CRC, colorectal cancer; CSF, cerebrospinal fluid; CTCs, circulating tumor cells; EAE, experimental autoimmune encephalomyelitis; EBV, Epstein-Barr virus; EDTA, ethylenediaminetetraacetic acid; EGF, epidermal growth factor; ENPP, ecto-nucleotide pyrophosphatase/phosphodiesterase; EOC, epithelial ovarian cancer; FRET, fluorescence resonance energy transfer; GBM, glioblastoma multiforme; GC, gastric cancer; GPCR, G protein-coupled receptor; HCC, hepatocellular cancer; HCV, hepatitis C virus; HRP, horseradish peroxidase; HVA, homovanillic acid; ICAM-1, intercellular adhesion molecule-1; IPF, idiopathic pulmonary fibrosis; ITD, internal tandem duplication; LC, lung cancer; LEDGF, lens epithelium-derived growth factor; LPA, lysophosphatidic acid; LPARs, LPA receptors; LPE, lysophosphatidylethanolamine; LPI, lysophosphatidylinositol; LPS, lysophosphatidylserine; LSECs, liver sinusoidal endothelial cells; LVD, lymphovascular vessel density; lysoPLD, lysophospholipase D; MCP-1, monocyte chemoattractant protein-1; MORFO, oligodendrocyte remodeling and focal adhesion organization domain; MS, multiple sclerosis; MVD, microvessel vascular density; NAD^+, nicotinamide adenine dinucleotide; NCI, National Cancer Institute; NSCLC, non-small-cell lung cancer; NUC, nuclease-like; OPN, osteopontin; PDE, phosphodiesterase; PDGF, platelet derived growth factor; PI3Kγ, phosphatidylinositol 3-kinase γ; pNP-TMP, thymidine 5'-monophosphate p-nitrophenyl ester; POSTN, periostin; RA, rheumatoid arthritis; RAC1, RAS-related C3 botulinum toxin substrate 1; ROS, reactive oxygen species; SMB, somatomedin B-like; SFs, synovial fluids; S1P, sphingosine 1-phosphate; SPC, sphingosylphosphorylcholine; TMZ, temozolomide; TNF, tumor necrosis factor; UDP-glucose, uridine diphosphate glucose; UPA, urokinase-type plasminogen activator; VEGF, vascular endothelial growth factor.

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1. Introduction

Autotaxin (ATX), originally isolated in 1992 [1] is a member of the nucleotide pyrophosphatase/phosphodiesterase family of ectoenzymes that hydrolyses phosphodiester bonds of various nucleotides [2], and it is also known as ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2 or NPP2). ATX possesses lysophospholipase D activity, catalyzing the hydrolysis of lysophosphatidylcholine (LPC, **1**) into lysophosphatidic acid (LPA, **2**) and choline (**3**) (Fig. 1) [3]. LPA is a bioactive phospholipid with diverse functions in almost every mammalian cell type, which exerts its action through binding to specific G protein-coupled receptors (GPCRs, specifically $LPAR_{1\text{-}6}$ in mammals) [4–6] and stimulates various cellular functions, including migration, proliferation and survival. Both ATX and LPA have attracted the interest of researchers in an effort to understand their roles in pathophysiology and to develop new agents to treat several pathological conditions, as has been discussed in various review articles [7–12]. The aim of this review article is to summarize the existing knowledge as to the implications of ATX in chronic inflammatory diseases and cancer and to highlight the low molecular weight compounds, which have been developed as leads for the discovery of novel drugs.

2. ATX, a lysophospholipase D enzyme

2.1. Isoforms, structure and catalytic mechanism

ATX, a ~125 kDa enzyme, is the best-characterized member of the nucleotide pyrophosphatase-/phosphodiesterase (ENPP) family, which consists of two main subgroups – namely ENPP1-3 and ENPP4-7 [2]. It is secreted as a constitutively catalytically active glycoprotein [13,14], while the other ENPPs are transmembrane or anchored proteins. ATX is the only member that exhibits extracellular lysophospholipase D (lysoPLD) activity and participates in LPA signaling.

The cDNA cloning of ATX in 1994 [15], which revealed its homology with phosphodiesterases, was followed by the cloning and tissue distribution of the three human and mouse isoforms (α, β, γ) in 2008 [16] and the additional two (δ and ε) in 2012 [17](Fig. 2). ATXα was the first identified isoform, originally isolated as an 'autocrine motility factor' from melanoma cells [1], that exhibits the lowest expression levels of all isoforms both in the central nervous system and the periphery [16,18]. ATXγ, the second discovered isoform – initially named as PD-I alpha [19,20], is expressed mostly in the central nervous system [16]. ATXβ, originally cloned from teratocarcinoma cells [16] and shown to

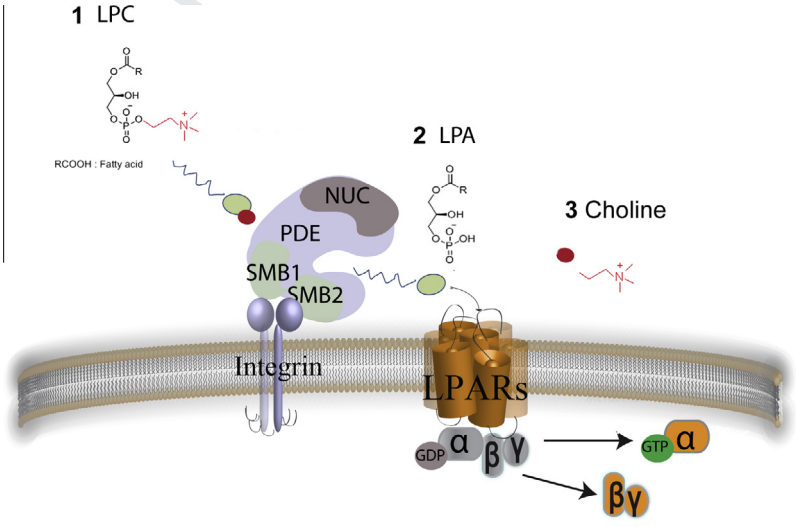

Fig. 1. ATX catalyzes LPC hydrolysis to LPA, activating its local LPA receptors and corresponding G-proteins.

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