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Review

Pleiotrophin and its receptor protein tyrosine phosphatase beta/zeta as regulators of angiogenesis and cancer

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ABSTRACT

Pleiotrophin (PTN) is a secreted heparin-binding growth factor that through its receptor protein tyrosine phosphatase beta/zeta (RPTPβ/ζ) has a significant regulatory effect on angiogenesis and cancer. PTN and RPTPβ/ζ are over-expressed in several types of human cancers and regulate important cancer cell functions *in vitro* and cancer growth *in vivo*. This review begins with a brief introduction of PTN and the regulation of its expression. PTN receptors are described with special emphasis on RPTPβ/ζ, which also interacts with and/or affects the function of other important targets for cancer therapy, such as vascular endothelial growth factor A, $\alpha_v\beta_3$ and cell surface nucleolin. PTN biological activities related to angiogenesis and cancer are extensively discussed. Finally, up to date approaches of targeting PTN or RPTPβ/ζ for cancer treatment are presented. Insights into the regulatory role of PTN/RPTPβ/ζ on angiogenesis will be extremely beneficial for future development of alternative anti-angiogenic approaches in cancer therapy.

Contents

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1. Introduction

Pleiotrophin (PTN) is a secreted polypeptide that together with midkine (MK) forms a two-member family of heparin-binding growth factors. PTN was initially reported as a neurite outgrowth promoting molecule, but has been also acknowledged as important for cell growth, migration and angiogenesis. It is highly expressed in the embryonic nervous system, as well as in the embryonic lung, kidney, gut and bone, and over-expressed in various tumor cell lines. PTN has been named in the past as p18, heparin-binding growth factor-8, heparin-binding growth-associated molecule, osteoblast-specific factor 1, heparin-binding neurotrophic factor and heparin affin regulatory peptide (reviewed in [1,2]).

2. PTN gene and protein

PTN protein is highly conserved among species, such as human, rat, mouse, chicken and bovine and homologues were recorded in frogs, insects and fish. PTN is highly homologous to midkine (MK); PTN and MK share 50% sequence identity and form a family of heparin-binding growth factors (reviewed in [1]). According to AceView, human *PTN* gene maps on chromosome 7, at 7q33, and contains nine distinct introns. Transcription produces nine different mRNAs, seven alternatively spliced variants and two unspliced forms, but only the six spliced mRNAs putatively encode proteins. The mRNAs appear to differ by truncation of the 5′ end, truncation of the 3′ end, presence or absence of a cassette exon, splicing *versus* retention of one intron. There are two probable alternative promoters, two non-overlapping alternative last exons and five validated alternative polyadenylation sites [3]. We mapped RNASeq data from the ENCODE database [4] in the region, and could verify 6 main coding exons in the human PTN gene and an extra exon found only in embryonic stem cells (ESCs) (Fig. 1), suggesting alternative splicing in ESCs, the function of which is non clarified.

The PTN protein that is mostly mentioned in the literature and whose tertiary structure has been clarified is the 136 amino acids protein, which consists of 24% of cationic residues, mainly lysines, organized in two beta sheet domains at the N- and C-terminal regions maintained through the formation of five disulfide bonds and connected by a flexible linker. Each of the domains possibly contains three antiparallel beta strands and possesses one thrombospondin type 1 (TSR-1) homology motif. Although both TSR-1 motifs have been initially implicated in PTN binding to heparin, the C-terminal TSR-1 domain has been reported as the main heparin-binding site. PTN possesses large basic surfaces on both of its structured domains, while the N- and C-terminal lysine-rich regions lack a detectable structure and appear to form random coils [1,2,5]. Besides heparin and heparan sulfate (HS), the C-terminal domain and hinge of PTN are also essential for maintaining stable interactions with chondroitin sulfate (CS) A and removal of the C-terminal tail weakens affinity for CS-A, but not for other CSs of high sulfation density, such as CS-E [5]. Three regions containing the K-R/K-X-R/K sequence have been mentioned as potentially responsible for protein access into the nucleus [2], although this has not been experimentally proven.

PTN protein is vulnerable to proteolytic activity, leading to peptides that may have similar or opposite to PTN biological functions. Plasmin leads to the production of five PTN peptides that correspond to distinct domains of the molecule and differentially affect *in vivo* and *in vitro* angiogenesis and modulate the angiogenic activity of vascular endothelial growth factor A (VEGF-A) in human endothelial cells [6]. Similarly, peptides produced *via* metalloproteinase (MMP) 2 cleavage of PTN stimulate or inhibit endothelial cell proliferation and migration through interference with VEGF-A activity [7].

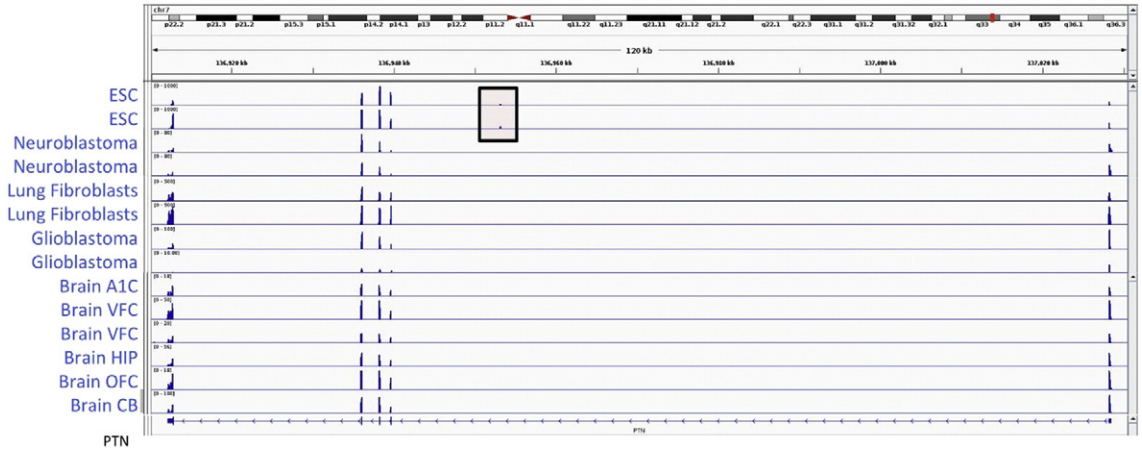

Fig. 1. Data from human genome (hg19 version) RNA-seq experiments were downloaded from the ENCODE database [4]. More specifically, H1esc (human esc cell line), NHLF (human lung fibroblasts) ".bigwig" files from Caltech and SK.N.SH (human neuroblastome cell line) and U87 (Glioblastoma cell line) ".bigwig" files from HAIB were used for graphic representation of PTN. In addition, ".bigwig" files were downloaded from the human brain atlas (http://download.alleninstitute.org/brainspan/MRF_BigWig_Gencode_v10/bigwig/) and different brain sections were used for the PTN gene expression calculation. IGV browser was used for visualization of the RNAseq .bigwig files. The Box indicates a non predicted exon found only in the ESC dataset. ESC, embryonic stem cells; A1C, primary auditory cortex; VCF, ventrolateral prefrontal cortex; HIP, hippocampus; OFC, orbital frontal cortex; CB, cerebellum.