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PAPP-A and the IGF system

La PAPP-A et le système des IGFs

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Abstract

Firstly discovered as a placental protein present abundantly in the circulation of pregnant women, pregnancy-associated plasma protein-A (PAPP-A) is widely expressed in multiple tissues. PAPP-A is a metalloproteinase that is able to specifically cleave three insulin-like growth factor binding proteins (IGFBPs): IGFBP-2, -4 and -5. PAPP-A binds tightly to glycosaminoglycans present on the surface of cells, thus functioning within tissues as a growth-promoting enzyme, releasing bioactive IGF in close proximity to the IGF receptor. Pro-MBP and stanniocalcin-2 (STC2) appear to be the main inhibitors of PAPP-A activity, by forming a covalent complex with the protease. According to in vivo experiments, IGFBP-4 is believed to be the main PAPP-A substrate to regulate IGF bioavailability. The regulation of PAPP-A includes transcriptional control of its gene, competing reactions with other IGFBPs potentially sequestering IGF from IGFBP-4 and hence antagonizing PAPP-A-mediated IGF activation, and proteolytic inhibition of PAPP-A. Finally, PAPP-A may serve as a therapeutic target to indirectly inhibit IGF signalling in tissues where this is driven by increased PAPP-A activity. By taking advantage of the intricate interaction between PAPP-A and IGFBP-4, highly specific and selective inhibition of PAPP-A is possible.

Keywords: Insulin-like growth factor (IGF); Insulin-like growth factor binding protein (IGFBP); Pappalysin; Pregnancy-associated plasma protein-A (PAPP-A); Proform of eosinophil major basic protein (pro-MBP); Stanniocalcin (STC)

Résumé

D'abord découvert comme une protéine placentaire abondamment présente dans la circulation de femmes enceintes, la protéine-A plasmatique associée à la grossesse (PAPP-A) est largement exprimée dans de multiples tissus. La PAPP-A est un métalloprotéase qui peut spécifiquement dégrader trois protéines de liaison des *insulin-like growth factors* (IGFBPs) : IGFBP-2,-4 et-5. La PAPP-A se fixe à des glycosaminoglycanes sur la surface de cellules, et fonctionne ainsi comme une enzyme favorisant la croissance dans les tissus, en rendant les IGFs biodiposnibles au niveau du récepteur de l'IGF-I. La pro-MBP et la stanniocalcin-2 (STC2) semblent être les inhibiteurs principaux de l'activité de la PAPP-A, en formant un complexe covalent avec la protéase. Selon des expériences in vivo, l'IGFBP-4 est supposé être le substrat principal de la PAPP-A pour moduler la biodisponibilité des IGFs. La régulation de la PAPP-A inclut le contrôle transcriptionnel de son gène, des réactions de compétition avec d'autres IGFBPs, isolant potentiellement les IGF et par conséquent l'activité de la PAPP-A (qui dépend de la présence d'IGFs), et l'inhibition de l'activité protéolytique de la PAPP-A. Finalement, la PAPP-A pourrait servir de cible thérapeutique pour indirectement inhiber l'activité des IGF dans les tissus où la protéase joue un rôle important. En profitant de l'interaction complexe entre PAPP-A et IGFBP-4, une inhibition spécifique et sélective de la PAPP-A est possible.

Mots clés : IGF, IGFBP, Protéine-A plasmatique (PAPP-A), Pappalysine, PAPP-A, Pro-MBP, Stanniocalcine

1. The (short) PAPP-A story

This story has been largely depicted in a recent [1], and will just be summarized here. Human pregnancy-associated plasma protein-A (PAPP-A) has been shown 40 years ago to be present

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at high levels in serum of pregnant women [2] without any demonstration of its biological function. The level of circulating PAPP-A is > 10,000-fold increased in pregnant women [3], not in pregnant mice, because PAPP-A is expressed in the human but not the murine placenta [4]. In the first trimester of Down's syndrome pregnancies, serum levels of PAPP-A are depressed [5], which is widely used in prenatal diagnosis.

The human PAPP-A sequence contains 1547 residues with a unique set of modules known from several different proteins (Fig. 1a). In serum of pregnant woman, the vast majority of PAPP-A is present in a heterotetrameric disulfide bound complex composed of two 200 kDa PAPP-A subunits and two subunits of proform of eosinophil major basic protein (pro-MBP), denoted PAPP-A/pro-MBP [6]. PAPP-A sequence contains a unique set of protein modules: a *N*-terminal 250-residue laminin G-like module, a 350-residue module containing the so-called elongated zinc binding consensus sequence characteristic of metzincins [7], and a *C*-terminal module that contains five short consensus repeat (SCR) modules, also known as complement control protein (CCP) modules. SCR3 and SCR4 bind glycosaminoglycans (GAGs) and mediate PAPP-A cell surface binding [8,9]. Within the metzincins, PAPP-A, its paralog PAPP-A2, and ulilysin, an archaeal proteinase of 29 kDa, comprise the pappalysin group, which does not share global similarity with any of the other member of the metzincin family. Finally, the PAPP-A subunit contains three Lin12-Notch repeat (LNR) modules, two of which within the proteolytic domain, and a third one located in the *C*-domain [10]. These LNR modules bind a calcium ion and are involved in determination of proteolytic specificity. Several experiments suggest a model in which the subunits of the PAPP-A dimer are arranged in an antiparallel manner, two putative LNR units being formed in *trans* (Fig. 1b).

2. PAPP-A is a protease of three IGFBPs

In 1999, it was shown that PAPP-A was responsible for the previously observed proteolytic activity towards insulin-like growth factor binding protein (IGFBP)-4 in fibroblast culture medium [13]. Thereafter, PAPP-A was subsequently shown to be the protease responsible for cleavage of IGFBP-4 in human, ovine, bovine, equine and porcine ovarian follicular fluid [14,15], and to be secreted from granulosa cells [16], vascular smooth muscle cells [17], and endometrial stromal cells [18]. It was later shown that IGFBP-2 [19] and IGFBP-5 [20] are also specifically cleaved by PAPP-A substrates. Importantly, while these IGFBPs are also cleaved by other proteinases, physiological cleavage of IGFBP-4 may be limited to PAPP-A [21,22]. IGFBP-3 and IGFBP-5 are also substrates of PAPP-A2 [23], and in the serum of pregnant woman, PAPP-A2 is responsible for the degradation of circulating IGFBP-5 [24]. The specificities of PAPP-A and PAPP-A2 towards the six different IGFBPs are summarized in Table 1.

PAPP-A cleaves these three IGFBP at single sites. IGFBP-4 is cleaved at Met-135/Lys-136 located in the linking domain [25], and IGFBP-2 between Gln165 and Met166 [19]. Cleavage allows dissociation of bound bioactive IGF, as individual *N*- and *C*-domains of IGFBPs have reduced affinity for the IGFs [21]. It is some basic amino acids of IGFBP-4 up to 16 residues

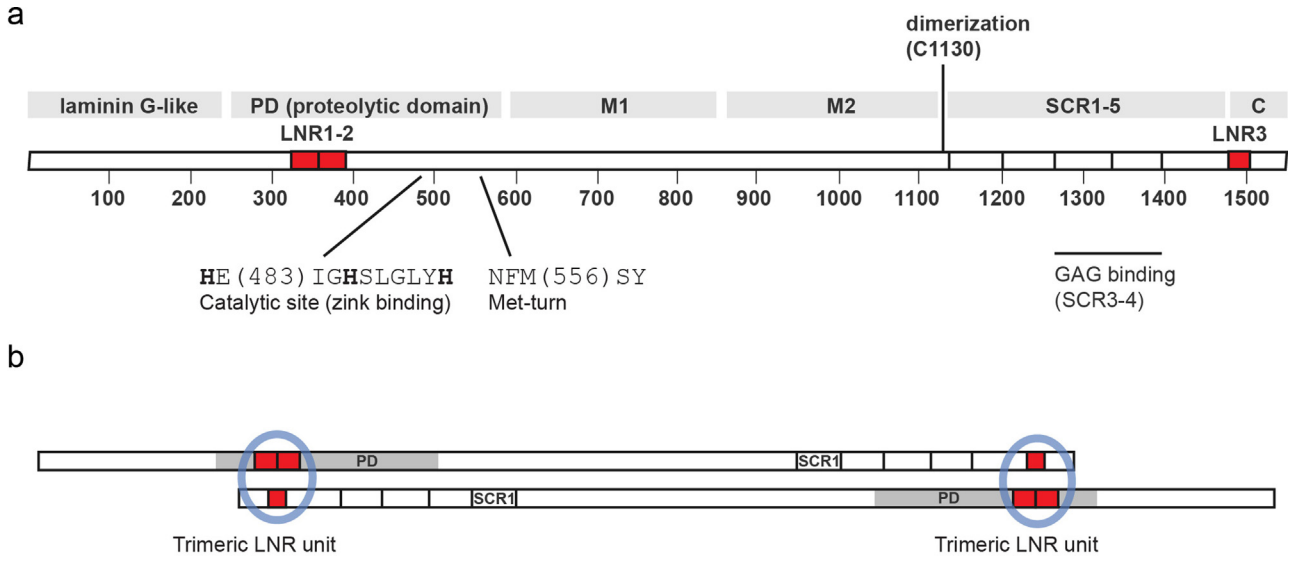

Fig. 1. Schematic overview of the primary structure of PAPP-A. a. The PAPP-A subunit is constituted by 1547 residues, 82 of which are cysteines. Protein modules are indicated with gray bars: the proteolytic domain (PD) of about 350 residues is preceded by a laminin G-like module of unknown function [7]. The PD contains the elongated zinc ion binding consensus sequence and a short sequence element responsible for formation of the Met-turn, both defining features of the metzincin superfamily of metalloproteinases [7]. Curiously, the second of the 22 exons of the *PAPP-A* gene encodes almost the entire laminin G-like module and approximately half of the PD [11]. The PD is followed by two ill-defined regions, tentatively designated M1 and M2 based on disulfide structure, and then by five short consensus repeats (SCR1-5), also known as CCP modules [11]. SCR3 and SCR4 bind glycosaminoglycans and are responsible for cell surface binding of PAPP-A [8]. In addition, note that the PAPP-A subunit contains three Lin12-Notch repeat (LNR) modules shown in red, two of which (LNR1-2) are located within the PD and a third (LNR3) located in the C domain. The LNR modules determine proteolytic specificity of PAPP-A [10]. b. PAPP-A exists as a 400 kDa dimer composed of two disulfide linked subunits. This simplified model highlights the antiparallel arrangement of the subunits and the two putative LNR units (blue circles), each formed from LNR1-2 in one subunit and LNR3 in the other [12].