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Review

New insights into the roles of SMB domains in the ENPP1 protein

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Abstract

ENPP1 (Ectonucleotide pyrophosphatase/phosphodiesterase 1) is a transmembrane enzyme with a short cytoplasmic region and a large extracellular domain consisting of two consecutive somatomedin (SMB) domains, a phosphodiesterase domain and a nuclease-like domain that lacks catalytic activity. It catalyzes the hydrolysis of ATP to AMP to produce extracellular inorganic pyrophosphate (PPi). By generating PPi, ENPP1 acts as a key regulator of tissue calcification and bone development. In humans, homozygous loss-of-function mutations in the phosphodiesterase domain and/or the nuclease domain of ENPP1 have been shown to cause several inherited disorders featuring either ectopic calcifications or abnormal calcium handling. While the catalytic domain of ENPP1 has been studied in some detail, the exact role of the two SMB domains remains unknown. This review aims to look behind the recent advances in our current understanding of the role of SMB domains in ENPP1 protein and outline for the first time the importance of these two domains in skin pigmentation. The SMB domains contain eight cysteine residues, each arranged in four disulphide bonds, and have been shown to mediate ENPP1 homo-dimerization through covalent cystine inter- and intra-molecular bonds. ENPP1 can inhibit insulin receptor autophosphorylation and downstream signaling through its SMB1 and SMB2 domains. Multiple mutations affecting conserved cysteines in the SMB domains have been identified to cause Cole disease, which is a rare skin pigmentation disorder. This interplay between ENPP1 and the insulin receptor may contribute to the pathogenesis of Cole disease and should be a future line of investigation.

Key words: *ENPP1, SMB domains, Cole disease, skin pigmentation*

1. Introduction

Ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), also called Plasma cell membrane glycoprotein 1 (PC-1) (Godingt 1987) is the first member of the ENPP family, which currently comprises seven ectoenzymes (ENPP1-7) (Stefan et al. 2005). ENPP1 is a type II transmembrane glycoprotein that exists as a homodimer of 230-260 kDa (Goldfine et al. 2008, Goldfine et al. 1998). It has a short cytoplasmic region and a large extracellular domain consisting of two consecutive somatomedin (SMB) domains, a phosphodiesterase domain and a nuclease-like domain that lacks catalytic activity (Figure 1a) (Goldfine et al. 2008, Goldfine et al. 1998). The phosphodiesterase domain cleaves a variety of chemical bonds including sugar-phosphate, pyrophosphate and phosphodiester bonds (Terkeltaub et al. 1994, Goding 2000). The major role of ENPP1 is to catalyze the hydrolysis of ATP to AMP, resulting in the production of extracellular inorganic pyrophosphate (PPi) (Stefan et al. 2005). ENPP1 acts as a key regulator of tissue calcification and bone development by modulating PPi levels. This is reflected by the phenotype of ttw/ttw (tiptoe walking) mice, which harbor a nonsense mutation in the ENPP1 sequence, resulting in a loss of more than one-third of the molecule and hence a disruption of ENPP1 protein function (Goding 2000). These mice lacking functional ENPP1 develop ectopic calcifications and osteoarthritic like symptoms.

In humans, homozygous loss-of-function mutations in *ENPP1* have been shown to cause several inherited disorders featuring either ectopic calcifications or abnormal calcium handling, including generalized arterial calcification of infancy (GACI: MIM 208000), pseudoxanthomaelasticum (MIM 264800), and autosomal recessive hypophosphatemic rickets type 2 (MIM 613312) (Terkeltaub et al. 1994, Nitschke et al. 2012, Jin et al. 2015, Lorenz-Depiereux et al. 2010). ENPP1 has also been associated with insulin resistance and/or obesity (Maddux et al. 1995, Bacci et al. 2005, Meyre et al. 2005, Wan et al. 2006, Gonzàlez-Sànchez et al. 2008).

One peculiar feature of ENPP1 is the presence of two SMB domains arranged in tandem without an intermediate spacer sequence within the extracellular domain (Figure 1a and b) (Gijsbers et al. 2003). While the catalytic domain of ENPP1 has been studied in some details, the exact role of the two SMB domains remains unknown. This study will focus on the recent advances in our current understanding of the role of SMB domains in ENPP1 protein and outline the importance of these two domains in Cole disease (MIM 615522) and skin pigmentation.

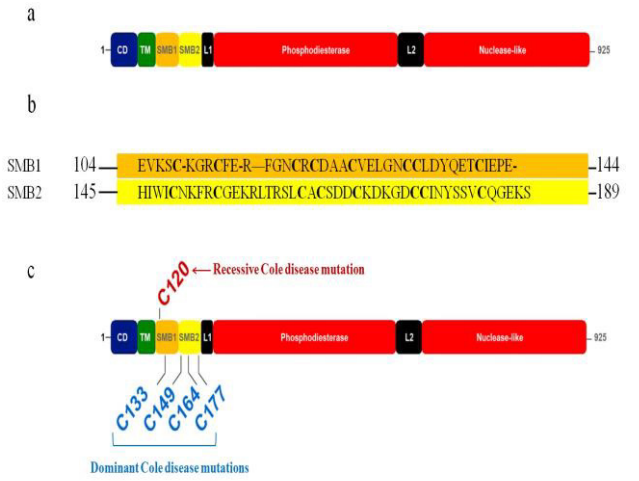

Figure 1: The structures of ENPP1 protein and SMB domains. (a) Structure of ENPP1 composed of cytoplasmic domain (CD), tansmembrane domain (TM) and a large extracellular domain consisting of two consecutive somatomedin (SMB) domains, a phosphodiesterase domain and a nuclease-like domain. (b) The pairing and spacing of the 8 cysteines of SMB domains of ENPP1 are conserved (in bold). (c) Comparison of recessive and dominant Cole disease mutated cysteines in SMB domains.

2. THE SOMATOMEDIN B (SMB) DOMAIN

Somatomedin B was originally identified as a serum peptide that is derived proteolytically from the N-terminus of the cell-surface adhesion protein vitronectin (Schvartz et al. 1999). In 2001, Dong. et al. resolved the disulfide configurations within the cysteine rich SMB domain (Kamikubo et al. 2002, Horn et al. 2004, Xu et al. 2001) via a crystal structure, and showed that the vitronectin SMB domain contains four disulfide bonds within 35 residues which are strictly conserved among the vitronectins from all known species (Xu et al. 2001).

To date, SMB domains have been identified in several other proteins but their function remains ill-defined. In the case of Vitronectin, the SMB domain mediates its binding with the urokinase receptor and plasminogen activator inhibitor- 1. The interaction with the urokinase receptor has been reported to affect cell migration and signal transduction (Schvartz et al. 1999), while the interaction with plasminogen activator inhibitor- 1 appears to stabilize it (Adhesion et al. 2006). Unlike vitronectin, the SMB domains of members 1–3 of ENPPs do not have any affinity for plasminogen activator inhibitor-1 or the urokinase receptor (Adhesion et al. 2006, Okumura et al. 2002).

3. ROLE OF SMB DOMAINS IN ENPP1 PROTEIN DIMERIZATION

ENPP1 like ENPP2 and ENPP3, is a homodimer of about 230-260 kDa (Goding 2000, Bollen et al. 2000). Each monomer consists of a short intracellular N-terminal domain required for targeting to the plasma membrane (Bello et al. 2001), a single transmembrane domain and a large extra- cellular portion encompassing the two consecutive SMB domains (SMB1 & SMB2), a catalytic domain and a poorly characterized C-terminal domain (Figure 1a). The secreted forms of NPP1–3 are believed to be generated by intracellular proteolysis somewhere near the SMB domains of the membrane-associated species (Sabina 1. BELLI 1993, Meerson et al. 1998).

The two SMB domains in ENPP1 contain eight cysteine residues (Figure 1b), each arranged in four disulphide bonds, and have been shown to mediate ENPP1 homo-dimerization through covalent cystine inter- and intra-molecular bonds (Gijsbers et al. 2003, Bellacchio 2012). The mechanism of the homo-dimerization is as yet unknown at the atomistic level. In 2003, Gijsbers et al. have found that the deletion of either the nuclease-like domain or both the catalytic and the nuclease-like domains did not hamper the ability of NPP1 to form dimers (Gijsbers et al. 2003). However, no dimers were detected after deletion of the SMB domains and their flanking sequences (Gijsbers et al. 2003). Moreover, the mere deletion of a single SMB domain did not affect dimerization (Gijsbers et al. 2003), suggesting that both SMB1 and SMB2 play a role in ENPP1 dimerization. The authors of this study have demonstrated that the conserved cysteines in both SMB domains of ENPP1 (cysteines 108, 112, 120, 122, 126, 132, 133, and 140 in SMB1; cysteines 149, 154, 164, 166, 170, 176, 177, and 184 in SMB2, (Figure 1b)) in addition to the two cysteines flanking the second SMB domain (Cys 195 and Cys 203) are necessary for homo-dimerization (Gijsbers et al. 2003). The conserved cysteine residues located within each SMB domain form the four disulfide bonds constituting the core of these domains and thus play a critical role in maintaining their structure and function. In 2012, Bellacchio et al. built a model of the tandem SMB domains of ENPP1 which revealed the presence of two large conserved surface patches not engaged in the inter-domain contact. The largest patch is flat and contains all the invariant positively charged residues characterized by fully solvent-exposed side chains within the tandem SMB domains, suggesting as a possible role its interaction with the negative phospholipids on the cell surface (Bellacchio 2012). Under this model, the SMB domains on ENPP1 work as binding modules that allow the molecular recognition of SMB domains from another membrane-bound ENPP1 molecule. As a result of this, the cysteines 195 and/or 203 flanking the SMB2 domains of each monomer are brought into close proximity, hence maximizing their chances to form disulfide bonds that will stabilizes the homodimer (Bellacchio 2012).

4. ROLE OF SMB DOMAINS IN ENPP1 INHIBITION OF INSULIN SIGNALING

Insulin resistance is a major contributor to type 2 diabetes and cardiovascular disease (Reaven 1988). The molecular mechanisms of insulin resistance are mostly unknown (Taniguchi et al. 2006). ENPP1 is a candidate molecule affecting this process as it can bind to the insulin receptor (IR) β-subunit and inhibit its autophosphorylation and downstream signaling (Betty A. Maddux and Ira D. Goldfin e 2000). ENPP1 over-expression affects insulin signaling and action in both cultured cells (Maddux et al. 1995, Betty A. Maddux and Ira D. Goldfin e 2000, Li et al. 2015) and rodent models (Dong et al. 2005, Maddux et al. 2006). In addition, increased ENPP1 expression has been observed in several tissues of insulin resistant subjects (Goldfine et al. 2008, Frittitta et al. 1997, Stentz and Kitabchi 2007). The notion that ENPP1 may play a role on human insulin resistance is further supported by the K173Q variant (commonly reported in articles as K121Q due to mis-assignment of the start codon during the initial studies on ENPP1) (Bacci et al. 2005, Frittitta et al. 2017). The Q121 variant was reported as a gain of function amino acid substitution with a stronger inhibitory activity on IR signaling (Maddux et al. 2006, Paola et al. 2011) and a genetic determinant of insulin resistance related abnormalities in several (Abate et al. 2014, Stolerman et al. 2008), although not all (Grarup et al. 2006), studies. This variant falls within the second SMB domain, but the underlying mechanism of pathogenicity is not yet well understood.

In 2013, Dimatteo et al. demonstrated that the inhibition exerted by ENPP1 on IR β-subunit autophosphorylation and downstream signaling is dependent upon the SMB1 and SMB2 regions (Dimatteo et al. 2013). They showed that in human insulin target cells, the SMB2, but not SMB1, domain takes part in ENPP1 dimerization (Dimatteo et al. 2013). The same study showed that neither SMB1 nor SMB2 affects the interaction between ENPP1 and IR (Betty A. Maddux and Ira D. Goldfin e 2000, Dimatteo et al. 2013). Since SMB 2 takes part in ENPP1 dimerization (Dimatteo et al. 2013), thus suggests a cause–effect relationship between ENPP1 dimerization and its inhibitory activity on insulin signaling. However, this was not the case for SMB 1, it is likely that the two domains partly act through different mechanisms on the deleterious role of ENPP1 on insulin signaling with only that of SMB 2 being mediated by protein dimerization.

5. CONSERVED CYSTEINE MUTATIONS IN SMB DOMAINS CAUSE SKIN PIGMENTATION ABNORMALITIES

To date, most of the reported germline mutations in the *ENPP1* gene are associated with GACI or autosomal recessive hypo-phosphatemic rickets type 2. These homozygous loss-of-function mutations affect either the active phosphodiesterase domain or the inactive nuclease domain of ENPP1 (Terkeltaub et al. 1994, Nitschke et al. 2012, Jin et al. 2015, Lorenz-Depiereux et al. 2010). Four heterozygous mutations affecting conserved cysteines in the SMB domain of ENPP1 have been reported as being causative for Cole disease (Figure 1c) (MIM 615522) (Eytan et al. 2013, NA et al. 2016), a genodermatosis featuring punctate palmoplantar keratosis, patchy hypo-pigmentation on the extremities, and in rare cases, cutaneous calcifications. Thus far, Cole disease has been reported to strictly follow a dominant mode of inheritance (Vignale et al. 2002, Mancini et al. 2009). Three of these conserved cysteines (p.Cys149, p.Cys164 and p.Cys177) (Figure 1b and c) lie in the SMB2 domain and completely segregate with dominant Cole disease (Eytan et al. 2013, NA et al. 2016). We recently identified an autosomal recessive disease characterized by the presence of hypo- and hyper-pigmented lesions over the body associated with punctate palmoplantar keratosis caused by a homozygous cysteine mutation (p.Cys120Arg) in the SMB1 domain of the ENPP1 protein (Figure 1b and c) (Chourabi et al. 2017). Due to the similarities in symptoms between prior descriptions of Cole disease and our patients' phenotype (Table 1) and the identification of cysteine-specific mutations in the same causative gene *ENPP1*, we reported this disorder as a recessive, and more extensive form of Cole disease (Chourabi et al. 2017). It is noteworthy that the p.Cys120 residue within SMB1 (Chourabi et al. 2017) is analogous in its position and disulfide bridging to p.Cys164 in SMB2 (Eytan et al. 2013), yet mutations in these two domains lead to distinct inheritance patterns (Eytan et al. 2013, Chourabi et al. 2017). These findings suggest that the two SMB domains are not equivalent and may play distinct roles in ENPP1 function. The germline Cys120Arg substitution that we identified within the SMB1 domain and other cysteine mutations in the SMB2 domain are associated with Cole disease, confirming that the two SMB domains of ENPP1 play a critical role in epidermal differentiation and skin pigmentation (Eytan et al. 2013, NA et al. 2016, Chourabi et al. 2017).

The SMB domains have been shown to mediate ENPP1 dimerization through covalent cystine inter- and intra-molecular bonds (Gijsbers et al. 2003, Bellacchio 2012). In our previous study we investigated the effect of the p.Cys120Arg and the p.Cys164Ser mutations on ENPP1 dimerization, and found that the p.Cys164Ser mutation responsible for dominant Cole disease severely affected dimer formation, while the p.Cys120Arg responsible for recessive Cole disease retained partial ENPP1 dimerization. The differential requirements for these analogous cysteines may explain the dominant versus recessive inheritance pattern of this disease. As mentioned in the previous section, ENPP1 can inhibit insulin receptor autophosphorylation and downstream signaling through its SMB1 and SMB2 domains (Dimatteo et al. 2013). This interplay between ENPP1 and the insulin receptor may contribute to the pathogenesis of Cole disease and should be a future line of investigation.

CONCLUSION

The SMB domain was first described as a serum peptide in victronectin protein (Schvartz et al. 1999), which interacts with the plasminogen activator inhibitor-1 or the urokinase receptor (Adhesion et al. 2006, Okumura et al. 2002). However, the SMB domains of ENPP1 do not have any affinity for these receptors. The SMB domains in ENPP1 have been shown to mediate its homo-dimerization and act as inhibitory domains in the context of IR β-subunit interaction which results in reduced IR autophosphorylation and downstream signaling. Mutations affecting conserved cysteines in SMB domains caused Cole disease, indicating that these two domains play a critical role in epidermal differentiation and skin pigmentation (Eytan et al. 2013, NA et al. 2016, Chourabi et al. 2017).

	Cole disease (MIM 615522)	
Inheritance	Autosomal Recessive	Autosomal Dominant
Age at onset	The first three months of life	Early onset (<1 year)
Lesions and Symptoms	- Hyper- and hypo-pigmented macules - Atopic eczema - Punctate palmoplantar keratosis	- Hypo-pigmented macules - Punctate palmoplantar keratosis
Location of lesions	The whole body except face	The extremities
Gene	*ENPP1* (6q23.2) SMB1 domain	*ENPP1* (6q23.2) SMB1 & SMB2 domain
References	(Chourabi et al. 2017)	(Eytan et al. 2013)(NA et al. 2016)

Table 1.Clinical presentation of Cole Disease

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