ChatGPT

PCOLCE (Procollagen C-Proteinase Enhancer) in Collagen Assembly and Fibrosis

Overview

Thesis: Procollagen C-endopeptidase enhancer 1 (PCOLCE, also known as PCPE-1) is a secreted glycoprotein that specifically accelerates the proteolytic maturation of fibrillar procollagens by bone morphogenetic protein-1 (BMP-1) and related enzymes, thereby promoting proper collagen fibril assembly [1] [2]. Discovered in the 1980s as a co-factor enhancing procollagen processing [3], PCPE-1 binds the C-propeptide of procollagen and the BMP-1 protease, organizing the collagen triple-helix for efficient C-terminal cleavage [4] [5]. This mechanism ensures timely conversion of procollagen to collagen, a rate-limiting step in fibrillogenesis [6] [4]. In pathological conditions, PCPE-1 is markedly upregulated in fibrotic tissues, tightly correlating with excessive collagen deposition [7] [8]. The following sections provide a structured overview: **(1.0)** PCPE-1's structure and binding properties, **(2.0)** its role in the collagen maturation process, and **(3.0)** its involvement in fibrosis as a potential biomarker and therapeutic target.

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graph TD
    Procollagen[Procollagen I/III trimer<br>(with C-propeptides)] -- binds -->
PCPE-1[[PCPE-1<br>(Enhancer protein)]]
    Procollagen -- substrate for --> BMP-1[(BMP-1<br>C-proteinase)]
    PCPE-1 -- bridges --> BMP-1
    PCPE-1 -- CUB domains bind --> Procollagen
    PCPE-1 -- NTR binds --> HSPG[(Syndecan HSPGs)]
    BMP-1 -- tethered by --> Fibronectin[(Fibronectin ECM)]
    PCPE-1 -- also binds --> Fibronectin
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graph LR
    A[Procollagen secreted<br>with propeptides] --> B[PCPE-1 attaches<br>to
procollagen C-propeptide]
    B --> C[BMP-1 cleaves C-propeptide<br>(PCPE-1 enhances efficiency)]
    C --> D[Tropocollagen released<br>& self-assembles into fibrils]
    D --> E[Collagen fibrils mature<br>(crosslinking and bundling)]
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1.0 PCPE-1 Structure and Binding Properties

¶1 Ordering: This section first outlines the identification and domain architecture of PCPE-1 (¶2), then details its binding interactions with collagen and protease partners that underlie its enhancer function (¶3).

¶2 Discovery & Composition: PCPE-1 was first identified in the mid-1980s as a protein co-purifying with procollagen C-proteinase activity, found to significantly increase the cleavage of type I procollagen's C-propeptide [3]. By the 1990s, the human PCOLCE gene (encoding PCPE-1) was cloned and characterized, revealing a secreted glycoprotein of ~55 kDa [9]. PCPE-1 is composed of two N-terminal CUB domains and one C-terminal netrin-like (NTR) domain [10], and it undergoes post-translational modifications (glycosylation, disulfide bonding) essential for proper folding and activity [11]. Notably, PCPE-1 itself has no enzymatic activity; its role is to bind procollagen and facilitate enzyme interaction [12] [13]. A homologous enhancer protein, PCPE-2 (gene *PCOLCE2*), shares the same domain structure but is less ubiquitously expressed and less studied in collagen metabolism [14] [15].

¶3 Binding Mechanism: The dual CUB domains of PCPE-1 bind tightly (sub-nanomolar *K*_D) to the C-propeptide region of fibrillar procollagens I–III [5]. This binding is calcium-dependent and positions PCPE-1 in a 1:1 stoichiometry on the procollagen triple helix [16] [17]. Meanwhile, the NTR domain mediates a weak but functionally important interaction with the BMP-1/tolloid protease [18]. The NTR also binds heparan sulfate proteoglycans (e.g. syndecan family) on cell surfaces and fibronectin in the extracellular matrix [19] [20]. Through these interactions, PCPE-1 is thought to localize and orient the collagen substrate and enzyme together at the pericellular matrix. Importantly, PCPE-1's action is highly specific: it accelerates C-terminal procollagen cleavage without affecting other BMP-1 substrates or interfering with other metalloproteinases [21]. This specificity allows PCPE-1 to boost collagen fibril formation selectively, ensuring fidelity of the collagen assembly process [1] [21].

2.0 Role in Collagen Maturation and Fibrillogenesis

¶1 Ordering: This section describes the normal process of collagen fibrillogenesis (¶2) and then explains how PCPE-1 accelerates the critical procollagen processing step to drive efficient fibril assembly (¶3).

¶2 Procollagen Processing: Fibrillar collagens (types I, II, III) are synthesized as procollagens, each polypeptide bearing N- and C-terminal propeptide extensions that keep the molecule soluble [2]. After secretion into the extracellular space, these propeptides must be removed to allow the collagen triple helices (tropocollagen) to spontaneously assemble into quarter-staggered fibrils [2]. The C-propeptide removal is a key rate-limiting step catalyzed by procollagen C-proteinases (primarily BMP-1 and related tolloid metalloproteinases) [1]. BMP-1 cleaves the C-propeptides of procollagens I–III, triggering rapid lateral assembly of the trimmed collagen molecules into fibrils. Proper timing of this cleavage is critical: premature or inefficient cleavage can disrupt fibril formation, whereas efficient processing promotes robust and organized fibrillogenesis.

¶3 PCPE-1 Enhancement Mechanism: PCPE-1 greatly boosts the efficiency of C-propeptide cleavage, effectively acting as a co-factor for BMP-1. Kinetic studies have shown that PCPE-1 can increase the catalytic efficiency (*k*_{cat}/*K*_M) of BMP-1 by roughly 12–15-fold on type I and III procollagens [4]. Mechanistically, the CUB domains of PCPE-1 bind the procollagen's C-propeptide "stalk" region near the BMP-1 cleavage site [5]. By anchoring to two of the three collagen chains, PCPE-1 induces a conformational distortion that exposes one chain's cleavage site to the protease [22] [23]. This oriented complex both increases BMP-1's binding affinity for the substrate and its turnover rate [4] [23]. Once BMP-1 cleaves the first procollagen chain, the remaining two chains are cleaved in succession (aided by the altered substrate geometry), yielding a fully processed tropocollagen trimer [24]. Throughout this process, PCPE-1 may also transiently interact with BMP-1's non-catalytic domains via its NTR domain, further stabilizing the enzyme–substrate complex [18] [25]. The end result is an accelerated and synchronized release of C-propeptides,

ensuring that collagen monomers are converted into fibrils efficiently during extracellular matrix assembly. Notably, PCPE-1's enhancer function is dedicated to collagen maturation – no other BMP-1-dependent proteolytic events are influenced by PCPE-1, preserving other extracellular matrix processes unaffected [21].

3.0 PCPE-1 in Fibrosis and Therapeutic Implications

¶1 Ordering: This section examines evidence linking PCPE-1 to fibrotic disease: first the overexpression of PCPE-1 observed in fibrotic tissues (¶2), then functional studies implicating PCPE-1 in fibrosis severity and its potential as a biomarker/therapeutic target (¶3).

¶2 Overexpression in Fibrotic Tissues: A growing body of research from the 1990s onward indicates that PCPE-1 is upregulated whenever pathological fibrosis occurs. Initial studies in 1997 showed that in a rat model of liver fibrosis (induced by chronic CCl_4 injury), hepatic stellate cells from cirrhotic livers had significantly higher *Pcolce* mRNA than those from healthy liver, and PCPE-1 protein became detectable in fibrotic liver tissue whereas it is normally absent in healthy liver [26]. Since then, many reports have found PCPE-1 over-expression to be a consistent feature of fibrosis across multiple organs [7] [8]. For example, in cardiac fibrosis models, PCPE-1 levels in the heart increase several-fold in response to pro-fibrotic stimuli like myocardial infarction or chronic hypertension, closely mirroring the rise in collagen type I deposition [27] [8]. Similar patterns are observed in lung, kidney, and skin fibrosis, where fibrotic lesions show elevated *PCOLCE* expression and protein levels compared to normal tissue [7] [28]. PCPE-1 upregulation often appears early in the fibrogenic process, making it a candidate early marker of active fibrosis [29] [30].

¶3 Functional Role and Target Potential: The correlation between PCPE-1 and fibrosis is not merely observational; recent functional studies suggest PCPE-1 actively contributes to fibrotic collagen accumulation. In one study, mice genetically deficient in PCPE-1 (Pcolce knockout) were protected from excessive collagen deposition in a diet-induced liver fibrosis model: despite similar injury (steatohepatitis), the $Pcolce^{-/-}$ mice developed significantly less collagen fibrosis than wild-type, with ~50% reduction in insoluble collagen content [31]. Notably, the absence of PCPE-1 did not alter upstream inflammatory or pro-fibrotic gene expression, indicating that PCPE-1 specifically affects the collagen maturation/extracellular matrix output of fibrosis rather than its initiation [31]. Consistent with these findings, human studies report that PCPE-1 protein is markedly elevated in end-stage fibrotic organs (e.g. cirrhotic livers of NASH or hepatitis patients) compared to non-fibrotic controls [32]. Together, these data implicate PCPE-1 as a pro-fibrotic factor that amplifies collagen buildup. Accordingly, there is considerable interest in PCPE-1 as both a fibrosis biomarker and a therapeutic target [21] [33]. Inhibiting PCPE-1's interaction with procollagen or with cell/ECM anchors could attenuate the reinforcement of collagen fibrogenesis, offering a novel anti-fibrotic strategy [33]. Likewise, measuring PCPE-1 levels in circulation or tissue might help in early detection or monitoring of fibrotic progression [34] [35]. In summary, PCOLCE/PCPE-1 plays a critical role in normal collagen assembly and, when dysregulated, in pathological fibrosis – making it a focal point for ongoing research into fibrosis diagnostics and therapy.

Sources: Adar *et al.*, 1986 [3]; Takahara *et al.*, 1995 [9]; Lagoutte *et al.*, 2021 [21] [7]; Weiss *et al.*, 2014 [1] [20]; Sansilvestri-Morel *et al.*, 2022 [31]; Ogata *et al.*, 1997 [26].

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