Periostin as a Heterofunctional Regulator of Cardiac Development and Disease

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Abstract: Periostin (Postn) is a heterofunctional secreted extracellular matrix (ECM) protein comprised of four fasciclin domains that promotes cellular adhesion and movement, as well as collagen fibrillogenesis. Postn is expressed in unique growth centers during embryonic development where it facilitates epithelial-mesenchymal transition (EMT) of select cell populations undergoing reorganization. In the heart, Postn is expressed in the developing valves, cardiac fibroblasts and in regions of the outflow track. In the adult, Postn expression is specifically induced in areas of tissue injury or areas with ongoing cellular reorganization. In the adult heart Postn is induced in the ventricles following myocardial infarction, pressure overload stimulation, or generalized cardiomyopathy. Here we will review the functional consequences associated with Postn induction in both the developing and adult heart. The majority of data collected to date suggest a common function for Postn in both development and disease as a potent inducible regulator of cellular reorganization and extracellular matrix homeostasis, although some alternate and controversial functions have also been ascribed to Postn, the validity of which will be discussed here.

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INTRODUCTION

In vertebrates four proteins containing fasciclin domains have been described, including Postn, Tgfbi (transforming growth factor-β (TGFβ))-inducible protein [also called Big-H3]), Stablin-1, and Stablin-2 [1]. Postn is a 90 kDa secreted protein that contains 4 repetitive fasciclin domains that are similar in sequence to the insect protein fasciclin [2]. Developmentally regulated differential splicing results in both matrix and membrane-associated (via amphipathic α-helix) and secreted isoforms. Postn is most closely related to Tgfbi, which like Postn is expressed in collagen-rich connective tissues, remodeling centers and valves, and is induced by TGFβ [3,4]. Fasciclin domain-containing proteins were first functionally characterized in the insect where fasciclin was shown to regulate axon guidance and homophilic cell-cell adhesion [2]. Whilst Postn and Tgfbi each contain 4 fasciclin-like adhesion domains and a single EMI protein-protein interaction module [5], only Tgfbi contains an RGD collagen-association motif [3,4]. Most fasciclin domain-containing proteins are GPI anchored and contain two or four copies of the domain that are thought to mediate cell adhesion through interaction with various integrins. The zebrafish genome also contains zPostn and zTgfbi homologues, and both zebrafish and mouse Postn and Tgfbi genes exhibit significant homology to Drosophila fasciclin-I [4], suggesting that the vertebrate genes are descendants of a common ancestral gene.

In contrast to the secreted Postn and Tgfbi proteins, the high molecular mass Stablin-1 (Stab-1) and Stablin-2 (Stab-2) proteins uniquely contain 7 fasciclin adhesion domains, numerous epidermal growth factor (EGF)-like domains, a link hyaluronan (HA)-binding domain, and a predicted transmembrane domain (Fig. 1A). While Stab-1 and Stab-2 are structurally similar, they appear to have unique functions as Stab-1 acts to clear unwanted self-molecules, while Stab-2 acts as a scavenger receptor for HA and AGE-modified proteins [6,7]. Both putative Stab-1 and Stab-2 receptors are expressed during development and within endothelial tissues and alternatively activated macrophages in the adult spleen, liver, lymph nodes and placenta. All four mammalian fasciclin domain-containing genes are expressed in the adult heart, whilst only Postn, Tgfbi and Stab-1 are present in the in utero developing heart (Fig. 1B-D) [4]. Even though several independent but complimentary Postn mice knockout studies have begun to shed light upon the requirement and possible function of Postn within the cardiovascular system, the roles of Tgfbi, Stab-1 and Stab-2 during cardiovascular development and heart homeostasis are presently unknown.

As a secreted ECM protein that associates with areas of fibrosis, Postn can directly interact with other ECM proteins such as fibronectin, tenascin-C, collagen I, collagen V, and
Postn can serve as a ligand for select integrins, such as \( \alpha_3 \), \( \alpha_5 \), and \( \alpha_6 \), where it can affect the ability of cells (fibroblasts or cancer cells) to migrate and/or undergo a EMT in select tissues during pathological disease progression [11,12]. However, it remains unclear whether this ligand-receptor association also occurs during normal homeostasis. Postn up regulation is also involved in cell survival and angiogenesis, and has become known as a promising marker for tumor progression in various types of human cancers [13-15].

**Postn EXPRESSION DURING HEART DEVELOPMENT**

Takeshita *et al.* originally cloned mouse Postn, which they designated *osteoblast-specific factor-2* (*OSF-2*), as it was robustly expressed within the osteoblastic MC3T3-E1 cells and bone samples [16]. Mouse and human Postn share 89.2% amino acid identity, suggesting a high degree of functional conservation. Postn shows a dynamic expression profile, both developmentally and in adult tissues that are undergoing remodeling or active stress. Postn is expressed in the developing endocardial cushions of the heart and the mature valves, the periosteum and periodontal ligament, injured vessels, tumors and metastatic cancer cells, and in cells undergoing EMT [11, 17-19]. With respect to cell type of expression, Postn appears to be expressed exclusively in endocardial cushion and fibroblast lineages, or in cells that adopt fibroblast-like characteristics following an injury event [8, 11, 20-23]. In addition to fibroblasts, Postn is expressed in other structures within the developing heart that may or may not be fibroblast in origin such as the valvular attachment apparatus, chordae tendineae and epicardial/pericardial structures, but is absent from the cardiomyocyte lineage itself [4, 10, 16, 17, 20, 21].
DEVELOPMENTAL DEFECTS ASSOCIATED WITH Postn DELETION IN MICE

To investigate the potential developmental functions of Postn, a gene deletion strategy was undertaken in mice in which the first exon was replaced with a lacZ reporter gene [24] or exons 4 through 10 encoding three of the 4 fasciclin domain sequences were deleted by insertion of a neomycin cassette [21]. Both mutants produced null alleles, and will hereafter be termed PostnlacZlacZ and PostnlacZlacZ mice. Although Postn is widely expressed in many developing organ systems, the majority of both PostnlacZlacZ and PostnlacZ mice survived well into adulthood, although they presented with smaller overall body weights. Even though ~14% of the PostnlacZlacZ mice die before weaning, the surviving PostnlacZlacZ mice develop an early-onset periodontal ligament (PDL) phenotype, with profound ultrastructural and histological changes in ameloblasts and enamel defects. PostnlacZlacZ mutants up regulate collagen III and exhibit a disorganized ameloblast layer that secretes an amorphous hypermineralized matrix. Significantly, placing PostnlacZlacZ mice on a soft diet reduced growth retardation, improved fertility and alleviated mechanical strain on the PDL but not postnatal lethality [24]. Subsequent deletion of Postn by another group also revealed a similar phenotype of smaller body size, as well as defective tooth development [9]. Ensuing analysis indicated PostnlacZlacZ mice exhibited severe periodontal defects after tooth eruption [25]. Interestingly, tooth clipping to remove masticatory forces rescued the periodontal defects. Using Flexicell culture apparatus to generate mechanical stress, Postn expression increased in strained PDL cells. This was preceded by a transient increase in Tgfb mRNA, and Postn elevation was blocked by addition of TGFβ-neutralizing antibodies [25]. Combined, these data suggest that Postn is essential for the proper function of the PDL during absorbance of strain and maintenance of the integrity in response to mechanical stresses.

CARDDIOVASCULAR PHENOTYPE OF MICE LACKING Postn

Analysis of the cardiovascular system in PostnlacZlacZ and PostnlacZ mice revealed neonatal valvular-dependent lethality in a minority of offspring, and latent disease with leaflet abnormalities in the viable majority of offspring [20, 26]. Surviving null leaflets are truncated, containing ectopic cardiomyocytes and smooth muscle, mis-expression of the cartilage proteoglycan aggrecan with disorganized matrix stratification. This phenotype is consistent with the islands/pockets of cartilage reported in adult valves including mice and human [20, 27, 28], and with the phenotype of Smad6+/- in which cartilage, bone, bone marrow, and even blood cells were formed within both AV and aortic valve leaflets [29]. Collectively, these findings suggest cushion cells are multipotential cells whose differentiation potential is normally restricted to primarily a fibroblastic lineage. Assessment of collagen production, 3D-lattice formation ability, and TGFβ responsiveness indicate that Postn-deficient fibroblasts are unable to support normal valvular remodeling [20]. Furthermore, null fibroblasts exhibit reduced ability to reorganize and contract 3D-collagen lattices, and a diminished response to increasing TGFβ concentrations. In fact, Postn can directly bind collagen type-I [10]. These observations collectively suggest that loss of Postn results in inappropriate differentiation of mesenchymal cushions and valvular abnormalities via a TGFβ-dependent pathway during establishment of mature valve leaflets.

Alk3 (type IA receptor for bone morphogenetic proteins (BMPs)) has been shown to be required for Postn expression in remodeling AV valves [30]. Postn was initially normally expressed in cGata6-Cre/Alk3 mutant E11.5 cushions but was appreciably reduced in mutant E14.5 atrioventricular (AV) leaflets. Given that TGFβ2 expression is also decreased in Alk3 +/- mutants [31], the cardiac cushions of mutant mice may therefore be hypoplastic secondary to decreased TGFβ2–mediated endocardial cushion EMT. In support of this, exogenous chick BMP2 or constitutively active Alk6 (type-IB BMP receptor) retrovirus significantly promoted expression of Postn in AV cushion explant assays [32]. As BMP2 has also been shown to induce TGFβ2 in this culture system [33] and BMP2 is known to function synergistically with TGFβ3 in the regulation of endocardial cushion EMT [34], BMPs may induce Postn by activating an endocardial TGFβ2 autocrine loop. In explanted diseased pediatric cardiac tissues from stenotic bicuspid aortic valves, Postn expression is largely absent from regions where ECM trilaminar stratification was lost, collagen fibrils disorganized and elastin fiber content reduced [20]. Combined with the mouse genetic disruption data, these results suggest that Postn may be required in utero for events that manifest themselves in postnatal and adult life. Specifically, Postn plays multiple roles as a primary responder molecule and may be linked to ECM deposition/re-organization during maturation and homeostasis of fibrous valve leaflets and maintenance of PDL integrity in response to mechanical stresses.

Connective tissue disorders are among the most common congenital defects in humans and constitute numerous adult diseases. Cardiac valve thickening and aortic dilation are major cardiovascular phenotypes of Marfans, and Marfans-like disorders, and are manifested through an alteration in collagen fibers and microfibril assembly [35]. Marfans patients have increased Postn protein as well as increased TGFβ and BMP signaling in their thickened heart valves, which suggests that Postn is positively regulated by TGFβ and BMP [36, 37]. Despite the complex and intriguing correlation of deregulated Postn expression levels in both normal and pathological transformation conditions, very little is known about how Postn is transcriptionally controlled. Thus, unraveling the molecular mechanisms that regulate Postn expression could prove insightful. For example, during osteoblast differentiation, transcription of Postn may be regulated by the bHLH transcription factor Twist, which itself is associated with EMT during tumor progression [38, 39]. A 3.9kb Postn proximal promoter region was isolated and shown to drive tissue-specific expression in the neural crest-derived Schwann cell lineage and in a subpopulation of Postn-expressing cells in the cardiac outflow tract and endocardial cushions [4]. Further analysis of the Postn promoter also implicated the ubiquitous transcription factor Ying Yang-1 (YY1) in regulating expression, which is interesting given YY1’s role as an initiator of tumorigenesis and inhibitor of important cell-cycle progression genes [40-42]. Thus, a better understanding of Postn transcriptional regulatory
mechanisms might also suggest additional molecular pathways that underlie its developmental functions.

**ROLE OF **Postn** IN ADULT HEART DISEASE**

It is likely that the developmental functions of Postn discussed above in facilitating proper organization of the ECM and in affecting cellular trafficking in remodeling hotspots is selectively re-employed in the adult organism. For example, Postn is expressed in collagen-rich connective tissues, remodeling centers, at sites of injury and inflammation, and is similarly induced by TGF-β [9, 13, 19-21, 43-45]. Specifically, myocardial infarction (MI) or pressure overload stimulation to the adult heart induces abundant re-expression of Postn from resident fibroblasts located between myocytes within the heart parachyma proper (Fig. 2A-C), where prior to such stimulation the major expression of Postn in the heart is within the collagen rich environment of the valves [20, 21, 45-48]. Postn expression is also induced at sites of vascular injury and hyperplasia [18, 49, 50], in the lung after injury/fibrosis [8, 51], in and around tumors [13], and at wound sites [52]. While not unequivocally proven, these various studies suggest a common biologic response whereby Postn becomes re-expressed at injury or inflammatory sites within the adult organism, often associated with a need for ECM and cellular migration, not unlike many developmental processes associated with Postn expression.

The heart contains a fibrosis skeleton of collagen and other ECM components that maintains overall ventricular geometries and the proper organization of myocytes within aligned strips that wrap around the heart for optimal force generation [53]. Remodeling of the fibrous skeleton and the ECM surrounding individual myocytes is critically involved in hypertrophic and dilatory growth of the heart in response to either pathologic or physiologic stimulation [53]. Long-standing pressure overload associated with hypertension, viral myocarditis, postpartum cardiomyopathy, and hypertrophic cardiomyopathy all induce significant alterations in the ECM and can lead to fibrotic heart disease and loss of ventricular compliance [54]. MI associated with occlusion of a major coronary artery leads to rapid cell death of an entire region of the ventricular wall or septum, resulting in an inflammatory response and subsequent formation of a fibrous scar that is rich in collagen but lacking in contractile capacity [55]. As discussed above, Postn is minimally expressed in the adult ventricles unless a pathologic stress or injury occurs. The function of Postn upon re-expression in the injured myocardium is currently an area of controversy given disparate accounts in the literature, although most reports suggest a function that is tied to the ECM, fibrotic remodeling, and the movement of cells through an injured or reorganizing area.

We reported that Postn−/− mice had an altered fibrotic response and were unable to form proper scars after MI injury, leading to greater rates of wall rupture and death [21], a result that was independently confirmed the following year in separately generated Postin null mice [45]. Conversely, we generated transgenic mice over expressing full-length Postn in the heart, which protected from wall rupture following MI injury [21]. Abundant Postn over expression in the heart did not induce fibrosis, although it did eventually promote a mild hypertrophy response that we interpret to be associated with integrin signaling (see below). Another interesting aspect of Postn−/− mice is that they were less susceptible to fibrotic heart disease associated with long-term pressure overload or MI, resulting in better ventricular performance [21]. These results suggest that loss of Postn is actually protective to the heart long-term, provided the initial insult is survived during the scar formation period if the insult was an MI (1-7 days)....
Three other groups have also attempted to alter expression of Postn or an alternately spliced isoform of Postn in the adult heart to examine its role in cardiac adaptation or mal-adaptation [23, 56, 57]. Katsuragi et al. attempted to augment or inhibit Postn expression in the adult rat heart using a plasmid DNA transfection protocol or a one-time infusion of antisense oligonucleotides, respectively [23]. Katsuragi et al. contended that using this method to over express Postn caused ventricular dilation and reduced cardiac function, although Postn protein expression was not examined, rendering these results difficult to interpret. This pathologic phenotype associated with Postn plasmid DNA transfection is also in stark contrast to data obtained in Postn over expressing transgenic mice, which showed no such effect, even at high levels of sustained expression for up to 12 months [21]. In another study, Litvin et al. injected an adenovirus encoding an alternatively spliced isoform of Postn (called PLF) into the heart, which after 7 days caused a minor increase in cardiac hypertrophy [56]. These results are consistent with Postn transgenic mice [21], although the adenoviral approach employed by Litvin et al. may have hastened the hypertrophic response due to the adenoviral infection itself. Thus, over expression of Postn is relatively innocuous to the adult heart, although it does eliminate rupture susceptibility following MI and it can produce a mild hypertrophy response with aging.

Results reported from a third group are perhaps the most controversial, as they suggest an entirely novel function for Postn in mediating cardiomyocyte proliferation and the subsequent repair of injured myocardium [57]. In addition to reporting increased proliferation, Kühn et al. claimed that Postn prevented fibrosis and reduced cardiac hypertrophy after an injury event, results that are not consistent with Oka et al. [21]. A potential reason for these differences may be that Kühn et al. utilized a recombinant truncated form of Postn (amino acids 22-669 of 811) in ascribing biological effects [57]. Using this partial protein, as well as a full-length protein, the authors reported increased proliferation rates in adult rat cardiac myocytes cultured for 9 days [57]. These later results may also be compromised given the known process of de-differentiation that occurs in adult myocytes cultured for this length of time, possibly rendering known process of de-differentiation that occurs in adult myocytes cultured for this length of time, possibly rendering these results difficult to interpret. This pathologic phenotype associated with Postn plasmid DNA transfection is also in stark contrast to data obtained in Postn over expressing transgenic mice, which showed no such effect, even at high levels of sustained expression for up to 12 months [21].

In a second potential mechanism whereby Postn affects the phenotype of the adult heart is by attachment-dependent signaling through cell adhesion molecules. Postn is an integrin binding protein and its attachment with fibroblasts or myocytes may impart a signal that affects how these cells perceive their environment and respond to stress or other remodeling signals. As mentioned earlier, Postn supports α2β1, α1β1, and α3β1 integrin attachment/signaling to facilitate EMT and metastatic activity [11, 59], as well as movement of cells within the developing bone centers and PDLs [11, 22, 9, 12, 24]. This integrin dependent interaction could impart a direct signal to cardiac myocytes that affects their hypertrophic growth or the milieu of other cells that surround myocytes and their paracrine signals. Alternatively, Postn...
might serve as a unique substrate for various inflammatory, mesenchymal, and stem cells to signal the need for repair in a given region of the myocardium based on unique integrin attachment properties. Finally, Postn might also signal through a homotypic interaction with the membrane bound fasciclin domain containing receptors Stab-1 or Stab-2 found on inflammatory or mesenchymal cells. Indeed, Stab-1 is highly expressed on macrophages and adjacent endothelial cells where it might be attracted to or modified within the injury area through a homotypic interaction with Postn and/or Tgfb1 [4, 60, 61].

It has also been reported that a “periostin-like factor” (PLF) may be overexpressed in failing human and rat cardiomyocytes and is localized to the cardiac myocyte itself [56]. However, PLF is actually one of four Postn isoforms expressed in the heart, and all four isoforms are missing in PostnlacZ/lacZ mice using a highly characterized antibody (Fig. 3A-D) [62]. This differentially spliced non-secreted isoform was originally identified by Kudo et al. [63]. Thus it is unclear why this particular Postn isoform was renamed PLF. Despite these issues, none of the alternately spliced isoforms off Postn are expressed in myocytes, and all appear to be exclusively made in fibroblasts from within the heart [10, 20, 21].

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Fig. (3). Comparison of Postn and PLF within PostnlacZ/lacZ nulls using antibodies directed against exon 21 (Postn-specific antibody) and Postn exon 17 (for PLF antibody). Brown staining shows positive immunohistochemistry for Postn or PLF. The results show that Postn is absent in adult cardiac myocytes (A) and null aorta (C), but that PLF antibody reactivity is detectable within PostnlacZ/lacZ knockout cardiac myocytes (B) and null aorta (D). These results suggest that the PLF antibody used by Litvin et al. [56] to claim myocyte-specific expression of PLF is likely due to one or more other non-specific proteins recognized by the PLF antibody or an unknown cryptic start site within the Postn C-terminus.
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