

Good example of 'discussion' research paper

[Sociology](#), [Violence](#)



Discussion

Periostin, an ECM protein, was named because of its expression in the periodontal ligament and periosteum of adult mice. 30 PN is expressed in tissue growth and remodeling, as in cardiac and valvular development and disease, wound repair, tumor tissues, and inflammation. 31-37 PN is also widely expressed in various atherosclerotic vascular lesions: it could be located in the intima, preatheroma regions, and the extracellular matrix of advanced lesions with calcification. PN variants are associated with extent of atherosclerosis in young persons, which suggest the importance of PN in the development of atherosclerosis in the arterial wall. 38, 39 This study used VSMCs derived from the thoracic aorta of PN-deficient mice to demonstrate that, while PN did not enhance VSMC proliferation without PDGF-BB stimulation, with that stimulation VSMC proliferation in PN-deficient mice was significantly inhibited. In addition, the concomitant inhibition of expression changes in cell cycle regulators further supports the hypothesis that PN is involved in VSMC proliferation. Cell cycle regulators whose increase is inhibited include SKP2, cyclin D1-CDK4, cyclin E-CDK2, PCNA and Rb activation. The decrease of both p27 and p21 levels are also inhibited in PN-deficient VSMCs. Also, it has been proven that PN enhanced migration of adult mice thoracic aortas SMCs in vitro. 15 These results indicate that PN could promote the migration and proliferation of VSMCs, perhaps synergistically with growth factors.

PDGF-BB plays an important role in vascular remodeling during cellular and extracellular responses to injury, 40, 41 inducing signaling for cell growth and migration through PDGFRs. 25, 42-43 Although there are two distinct

PDGFRs: PDGFR- α and - β , a lack of functional PDGFR- α in VSMCs has been reported. 44 We also used immunoblotting to detect PDGFR- β , but not PDGFR- α . While the level of PDGFR- β expression was not altered in PN-deficient VSMCs, their PDGFR- β autophosphorylation at Tyr751 decreased from 1 minute to 30 minutes after PDGF-BB stimulation when comparing to those of WT VSMCs. It has been suggested that PDGFR- β mediates different signaling pathways which regulate the proliferative and the migratory responses to PDGF-BB, with MAPK, Src and JNK regulating proliferation and FAK and Akt regulating migration. 7, 15, 45-48 This study showed that PN-deficiency inhibited PDGFR- β phosphorylation, that this effect was associated with the inhibition of downstream ERK1/2, JNK, Src and Akt receptor-triggered signaling events, as well as the reduction of FAK phosphorylation. It suggests that the inhibition of PDGFR- β activation and downstream signaling pathways may be a major mechanism of growth suppression by PN-deficiency, and that PN-deficiency likely acts by impairing the response capacity of PDGFR- β to PDGF-BB stimulation. PN belongs to a class of ECM, which previous studies have shown to be closely associated with crosstalks between PDGFR- β and integrins. 28, 29, 49, 50 We therefore speculate that a PDGFR- β -integrins crosstalk mechanism could also be involved in the inhibitory effect of PN-deficiency toward PDGFR- β . Further, studies have shown that mice deficient in PDGFR- β die perinatally with several anatomical and histological abnormalities. Further, glomerular tufts are not formed, and a few distended capillary loops fill that space. Therefore, the role of PN-deficiency states needs to be further explored urinary diseases. This was further corroborated by another study by .

It has been reported that SMC upregulates the expression of integrin $\alpha 5\beta 1$ and $\alpha V\beta 3$ during neointimal formation after balloon injury to rat carotid artery, 51-53 and that inhibition of integrin $\alpha V\beta 3$ of SMCs leads to prevention of neointimal hyperplasia. 54-57 Previous studies also indicate that the $\beta 1$ integrin subunit and $\alpha V\beta 3$ -integrin can influence PDGFR- β activity. 12-14, 45 In addition, our previous study has shown that PN mediates vascular SMC migration through an interaction with αV -integrins (mainly $\alpha v\beta 3$).

15Therefore, we examined the PDGF-BB-stimulated association of PDGFR- β with integrin $\alpha V\beta 3$ and $\alpha 5\beta 1$ by immunoprecipitation using antibodies specific to $\alpha V\beta 3$ and $\alpha 5\beta 1$. PN-deficiency inhibited the amount of PDGFR- β co-precipitated with $\alpha 5\beta 1$, but not with $\alpha V\beta 3$. This indicates that the inhibitory effect of PN-deficiency on PDGF-BB-induced VSMC proliferation may be initiated by blocking the crosstalk of $\alpha 5\beta 1$ -integrin, but not $\alpha V\beta 3$ -integrin, with PDGFR- β . It has been further confirmed that PDGFR- β and $\alpha 5\beta 1$ -integrin together control the migration of mesenchymal stem cells. The physical proximity of $\alpha 5\beta 1$ -integrin with PDGFR- β might facilitate the recruitment of numerous shared signaling and adapter proteins; the potentiation of FAK, Akt, Erk1/2, JNK and Src activity by crosstalk between $\alpha 5\beta 1$ -integrin and PDGFR- β is an essential event in the cascade that induces cell motility and proliferation. Thus, PN controls VSMC proliferation and inhibits neointima formation through crosstalk with the potent vascular receptor PDGFR- β and $\alpha 5\beta 1$ -integrin.

Our study is the first to provide several lines of evidence demonstrating a significant role for PN in regulating VSMC proliferation in vitro and neointima formation in vivo. (1) VSMCs isolated from PN-/- mice exhibit a significantly

reduced ability to proliferate in vitro, accompanied by significant change in the level of cell cycle regulators. (2) PN-deficiency results in a cascade of PDGFR- β inhibition and downstream signaling pathways. (3) PDGF-BB stimulation initiates PDGFR- β and $\alpha 5\beta 1$ -integrin crosstalk, which requires PN. (4) PN-/- mice exhibit dramatically relieved neointima formation after a carotid artery wire injury. Although it is well known that different ECM proteins can stimulate VSMC migration, 58-59 our present study extends previous research by demonstrating that PN-deficiency has an inhibitory effect on PDGF-BB-stimulated VSMC proliferation in vitro, a mechanism that is closely related to PDGFR- β inhibition and downstream signaling pathways. Despite the crucial importance of PDGFR- β in directing vascular cell behavior is well documented, the PN-dependent mechanisms that regulate its signaling have not been reported before. Little is known about whether and which integrin receptor(s) is involved in the effect of PN-deficiency on PDGF-BB-induced PDGFR- β signaling. Using VSMCs of PN-deficient mice, we have shown that proliferation of VSMCs in vitro require crosstalks of PN-PDGFR- β - $\alpha 5\beta 1$, but not PN-PDGFR- β - $\alpha V\beta 3$. Further, it has been found that cell surface tissue transglutaminase (tTG) induces clustering of integrins and amplifies integrin signaling by acting as an integrin binding adhesion co-receptor for fibronectin. Also, it has been found that the integrin associated signaling renders cells more resistant to genotoxic anti-cancer agents like ionizing radiation and chemotherapeutic substances. This raises the scope of this study to include cancer research, as well as therapeutics.

In conclusion, the present study demonstrates for the first time that PN-deficiency plays a significant negative role in VSMC proliferation induced

either by PDGF-BB stimulation or mechanic injury, through interaction with $\alpha 5\beta 1$ -integrin (but not $\alpha V\beta 3$ -integrin) and subsequent inhibition of PDGFR- β signaling cascade. PN could provide a target for future therapeutic and diagnostic approaches in neointima after vascular injuries.

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