



Mothers against decapentaplegic homolog 4 as a proteomic hub in vascular remodeling and residual cardiovascular risk

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Abstract

Translational cardiovascular medicine increasingly relies on systems-level approaches to uncover therapeutic targets that bridge molecular mechanisms and clinical outcomes. Recent proteomic analyses in experimental myocardial infarction models highlight how modulation of multiple protein networks can confer cardioprotection, emphasizing the complexity of post-infarction remodeling. Among this systems framework, mothers against decapentaplegic homolog 4 (SMAD4) has emerged as a pivotal mediator of transforming growth factor- β /bone morphogenetic protein signaling, integrating hemodynamic forces with endothelial, smooth muscle, and extracellular matrix responses. Experimental evidence demonstrates that SMAD4 governs endothelial mechanotransduction, vascular smooth muscle cell phenotype, fibrosis, and inflammation, while its loss promotes vascular instability, arteriovenous malformations and pulmonary vascular remodeling. High-throughput proteomics highlights SMAD4 as a network hub regulating cytoskeletal organization, oxidative stress, and extracellular matrix dynamics, providing mechanistic insight into processes contributing to plaque vulnerability and residual cardiovascular risk. Although not yet validated as a circulating biomarker, SMAD4 expression in vascular and immune cells may complement established markers such as low-density lipoprotein cholesterol and high-sensitivity C-reactive protein when integrated within multi-marker proteomic and artificial intelligence-assisted risk models. Therapeutically, cell-specific SMAD4 modulation, RNA-based strategies, and targeted interference with upstream signaling represent promising avenues for precision cardiology.

Key Words: Atherothrombosis; Biomarkers; Endothelial dysfunction; Precision cardiology; Proteomics; Residual cardiovascular risk; Mothers against decapentaplegic homolog 4;

Core Tip: Proteomics is reshaping cardiovascular medicine by revealing network-level molecular mechanisms underlying myocardial infarction and atherothrombosis. Among emerging targets, mothers against decapentaplegic homolog 4 (SMAD4), a central mediator of transforming growth factor- β /bone morphogenetic protein signaling, has gained attention as an interesting regulator linking disturbed flow, inflammation, fibrosis, and vascular remodeling across endothelial and smooth muscle cells. Although not yet supported by large randomized trials, SMAD4 represents a proteomic network hub that may complement established biomarkers such as low-density lipoprotein cholesterol and high-sensitivity C-reactive protein. Integrated within multi-protein signatures and artificial intelligence-based models, SMAD4 may contribute to improved prediction of residual cardiovascular risk and precision phenotyping.

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INTRODUCTION

Translational cardiovascular medicine is entering a decisive phase in which systems-level methodologies, particularly genomics, proteomics, and advanced bioinformatics, are redefining our understanding of molecular networks that underlie disease pathogenesis and therapeutic response, moving beyond single-target interventions to an integrated approach of cardiovascular disease[1]. In the context of myocardial infarction (MI) and atherothrombosis, proteomic analyses have revealed that cardioprotection is often mediated by the coordinated modulation of multiple protein pathways, reflecting both the complexity of post-infarction remodeling and the limitations of reductionist strategies. High-throughput proteomic platforms now allow simultaneous quantification of thousands of proteins, revealing integrated molecular adaptations across metabolic, structural, inflammatory, and endothelial compartments following MI [2]. These insights underscore how post-MI remodeling is not governed by isolated pathways but by tightly interconnected molecular networks whose interactions shape cardiomyocyte survival, extracellular matrix (ECM) dynamics and endothelial integrity[3].

This framework is reinforced by the recent proteomics-based study by Zhao *et al*[4], which demonstrated how Agari-5 therapy exerts cardioprotective effects in MI rats through multi-target modulation of the proteome. Their analysis identified 60 differentially expressed proteins, four of which were directly associated with cardiac tissue: Phosphoserine aminotransferase 1 (PSAT1), 3-phosphoinositide-dependent protein kinase-1 (PDK1), stromal cell-derived factor 1 (SDF2) and mothers against decapentaplegic homolog 4 (SMAD4). The coordinated regulation of these proteins, each belonging to distinct functional pathways [metabolic regulation, mitochondrial signaling, transforming growth factor- β (TGF- β) and bone morphogenetic protein (BMP) signaling axis and endoplasmic reticulum stress response], exemplifies the principle that effective cardioprotection emerges from systems-level molecular modulation rather than from single-target interventions. Preclinical studies show that increased PSAT1 expression in the post-infarction myocardium promotes cardiomyocyte proliferation, reduces fibrosis, and improves cardiac function, suggesting a beneficial role in cardiac remodeling and repair after ischemic injury[5]. Reduced PDK1 expression is associated with heart failure in both murine models and human cardiac tissue. PDK1 deficiency induces apoptosis, oxidative stress, and metabolic alterations, leading to cardiac dysfunction. In patients with heart failure, PDK1 is significantly downregulated, and its loss correlates with worsening ventricular function and adverse outcomes[6]. No cohort studies currently link SDF2 levels directly with cardiac outcomes. However, for the related protein SDF-1, elevated plasma levels are associated with increased risk of heart failure and mortality in the general population, as demonstrated by the Framingham study[7].

SMAD4 AS A SYSTEMS-LEVEL REGULATOR

Within this expanding molecular landscape, the TGF- β /BMP signaling axis has regained prominence for its central role in vascular development, homeostasis, and disease. At the core of these pathways lies SMAD4, the common-mediator SMAD that orchestrates nuclear translocation and transcriptional activity of receptor-activated SMAD2/3 and SMAD1/5/8[8,9]. While its importance in oncogenesis and developmental biology is already established[10], its emerging contribution to cardiovascular pathophysiology has only recently begun to emerge.

Recent experimental evidence, combined with proteomics-guided analyses, positions SMAD4 as a nodal regulator of endothelial activation, vascular smooth muscle cell (VSMC) phenotype, ECM remodeling, mechanotransduction, and inflammation, processes intimately linked to atherothrombosis and residual cardiovascular risk. Consistently,

intermittent hypoxia has been shown to upregulate SMAD4 through NLRP3-mediated mechanisms, providing a direct pathophysiological link between SMAD4, inflammatory activation, and heightened vascular risk[11].

Moreover, cardiomyocyte-specific SMAD4 knockout induces cardiac hypertrophy, fibrosis, and heart failure *via* hyperactivation of MEK1-ERK1/2 signaling[12], reaffirming its broad impact across cardiovascular tissues. In murine models, SMAD4 loss is associated with early mortality and pathological remodeling, while in humans, dysregulation of TGF- β /SMAD4 signaling has been implicated in fibrotic progression and heart failure[7,13].

The rise of proteome-centered cardiology has further highlighted how dysregulated SMAD4 signaling may influence plaque vulnerability, vascular biology, fibrotic remodeling, and flow-dependent vascular inflammation in a way not readily captured by conventional biomarkers. In this context, SMAD4 offers a compelling opportunity to translate systems-level molecular insights into clinically meaningful biomarkers and therapeutic strategies. This editorial highlights how proteomics can uncover nodal points of vulnerability and therapeutic opportunity, offering a mechanistic map for precision cardiovascular therapeutics.

Biology, mechanotransduction, and endothelial dysfunction

SMAD4 is a central mediator of TGF- β /BMP signaling and plays a critical role in vascular remodeling, endothelial and smooth muscle cell function, and the maintenance of vascular integrity. Proteomics-guided studies have identified SMAD4 as a key node integrating hemodynamic forces and molecular signaling to regulate endothelial cell responses and vascular stability[14]. Conditional deletion leads to reduced vessel sprouting, impaired tube formation, and defective interactions with mural cells[15]. These defects are accompanied by dysregulated expression of angiopoietins, adhesion molecules, and gap-junction proteins.

Importantly, SMAD4 activity is modulated by mechanical forces. Regions of arteries exposed to disturbed or oscillatory shear stress, canonical sites of atheroma development, exhibit altered SMAD4-driven transcriptional responses. Proteomic and transcriptomic data show that disturbed flow promotes SMAD4-dependent endothelial activation, leukocyte adhesion, ECM remodeling, and endothelial-to-mesenchymal transition, all contributing to vulnerable plaque formation.

SMAD4 integrates TGF- β /BMP9/10 signaling with fluid shear stress, enabling endothelial cells to sense and adapt to mechanical cues. Loss of SMAD4 in endothelial cells disrupts the fluid shear stress set point, leading to excessive oscillatory flow-mediated endothelial proliferation, loss of arterial identity, and the formation of arteriovenous malformations (AVMs) through dysregulated KLF4-TIE2-PI3K/Akt signaling and repression of CDK inhibitors[16]. SMAD4 also directly represses angiopoietin-2 (ANGPT2) transcription; its loss increases ANGPT2, promoting AVMs formation and abnormal vessel morphology, which can be rescued by ANGPT2 inhibition[17]. Ligand binding induces phosphorylation of R-SMADs, which heterotrimerize with SMAD4 and translocate to the nucleus to regulate genes controlling proliferation, apoptosis, differentiation, and ECM remodeling[13]. SMAD4 stability is further regulated by post-translational modifications such as O-GlcNAcylation, which prevents proteasomal degradation and sustains TGF- β signaling[18].

Furthermore, SMAD4 functions as the obligate co-mediator required for nuclear translocation and transcriptional activity of receptor-regulated SMAD2/3. Through this mechanism, it orchestrates the transcriptional programmes governing endothelial function, VSMC phenotype, ECM composition, and inflammatory responses.

Consistent with this central regulatory role, SMAD4 deficiency in VSMCs as well as SMAD4 functional variants impair differentiation, proliferation, and ECM maintenance, thereby predisposing to aortic aneurysm and dissection *via* increased apoptosis, protease activity, and inflammation[19,20], while endothelial SMAD4 loss promotes vascular inflammation, oxidative stress, and endothelial dysfunction, contributing to hypertension and pulmonary hypertension by impairing cell adhesion and ECM organization[21,22].

The involvement of SMAD4 in smooth muscle biology adds another layer of relevance. VSMC phenotypic switching, fibrosis, and microcalcification, all decisive factors in plaque evolution, are shaped by SMAD4-mediated transcriptional signaling[23]. Together, these findings suggest that SMAD4 integrates hemodynamic stress, inflammatory stimuli, and tissue remodeling within a unified molecular framework. These mechanotransduction features parallel other endothelial proteins such as junctional cadherin 5 associated (JCAD)[24,25], which also links disturbed flow to endothelial activation, inflammation, and thrombotic priming, emphasizing the importance of proteomic approaches in uncovering mechanosensitive regulators of vascular disease.

SMAD4 and residual cardiovascular risk

Residual cardiovascular risk remains a major challenge in contemporary cardiology. Despite optimal control of low-density lipoproteins cholesterol (LDL-C), blood pressure, and systemic inflammation, many patients continue to experience recurrent ischemic events. This persistent risk reflects biological processes that are not fully captured by traditional biomarkers, processes such as endothelial dysfunction, impaired mechanotransduction, fibrosis, and maladaptive vascular remodeling.

SMAD4 sits at the intersection of these pathways. By regulating inflammatory and fibrotic signaling, SMAD4 influences plaque stability and vascular adaptation to mechanical forces[26]. Dysregulated SMAD4 activity may promote fibrotic plaque evolution, ECM disorganization, and reduced vascular compliance, ultimately increasing susceptibility to ischemia and thrombosis. Clinically, elevated SMAD4 expression in circulating monocytes has been proposed as a biomarker for increased atherosclerosis risk, particularly in patients with comorbidities such as obstructive sleep apnea, linking intermittent hypoxia, NLRP3 activation, and vascular inflammation[11].

Although SMAD4 has not yet been fully established as a circulating biomarker, its proteomic and mechanistic profile suggests that it may provide complementary information to conventional markers such as LDL-C, high-sensitivity C-reactive protein (hs-CRP), and troponin. As with JCAD, which has recently emerged as a biomarker of endothelial-derived thrombotic risk[25], SMAD4 may help identify patients whose residual cardiovascular risk stems from fibrotic remodeling or hemodynamic stress-related vascular dysfunction. Importantly, current evidence supporting SMAD4 as a

cardiovascular risk marker is derived primarily from limited experimental models; robust randomized controlled trials and systematic meta-analyses are lacking, precluding its validation as a clinical biomarker at this stage.

Therapeutic potential: A target for precision cardiology?

Given its central position within TGF- β signaling, SMAD4 represents an appealing but challenging therapeutic target. Conceptually, strategies could include pharmacologic selective inhibition of SMAD nuclear transport[27], endothelial- or VSMC-specific RNA-based therapies[21], modulation of upstream regulators (*e.g.*, ALK5 and PI3K/Akt inhibitors)[16], microRNAs or endothelial-targeted nanoparticle platforms for localized delivery[28,29]. These strategies would complement, not replace, existing interventions: Lipid-lowering therapies reduce cholesterol burden, anti-inflammatory agents modulate cytokine signaling, and antiplatelet drugs reduce activation and thrombus formation, but none restore physiological endothelial mechanotransduction or normalize fibrinolytic imbalance at sites of disturbed flow. While SMAD4 has not yet been validated as a circulating biomarker or therapeutic target in clinical practice, its identification as a proteomic network hub provides a strong rationale for future prospective studies and clinical validation. Despite the promise of SMAD4 as a therapeutic target, several challenges remain. First, the evidence supporting SMAD4 as a biomarker or therapeutic target is primarily derived from experimental models, proteomics-driven network analyses, and limited observational human data. No randomized controlled trials, large prospective cohorts, or systematic meta-analyses currently validate SMAD4 for clinical risk assessment or therapeutic decision-making. Second, the dynamic mechanosensitivity complicates its targeting, and the redundancy of endothelial signaling pathways may limit the efficacy of single-agent interventions. Moreover, the lack of standardized assays for SMAD4 quantification limits cross-study comparability.

Importantly, SMAD4 is unlikely to function as a standalone marker in clinical practice. Its greatest potential lies in integration within multi-protein signatures that capture endothelial dysfunction, inflammation, fibrosis, and mechanotransduction. Advances in high-throughput proteomics, combined with artificial intelligence (AI) and machine-learning approaches, may enable the development of composite risk models that incorporate SMAD4 alongside other cardiovascular proteomic biomarkers. Such integrative frameworks could improve patient stratification, identify residual cardiovascular risk not captured by LDL-C or hs-CRP, and guide precision therapeutic strategies. Future studies should focus on multi-omics integration, AI-based predictive modeling, and prospective clinical validation to translate these systems-level insights into practical cardiovascular care. While all current evidence remains preclinical and must therefore be interpreted cautiously, these findings highlight the potential of proteomics to reveal molecular hubs that may guide precision therapeutics in the future.

CONCLUSION

SMAD4 is emerging as a central regulator of vascular homeostasis, integrating mechanical forces, inflammatory signaling, and fibrotic remodeling across endothelial and smooth muscle compartments. Proteomic data reveal a broad network of SMAD4-dependent pathways that may significantly influence vascular biology and residual cardiovascular risk. However, current evidence remains exploratory and hypothesis-generating, and SMAD4 cannot yet be considered a validated clinical biomarker or therapeutic target. While much work remains to translate these insights into clinical practice, the convergence of proteomics, vascular biology, and therapeutic innovation positions SMAD4 as a promising candidate for future risk stratification and targeted intervention. Rather than functioning as a standalone marker, the future relevance of SMAD4 lies in its integration within multi-proteomic signatures analyzed through AI and machine-learning approaches, enabling improved cardiovascular risk stratification and precision phenotyping beyond conventional biomarkers such as LDL-C and hs-CRP. Rigorous prospective studies, randomized trials, and meta-analytic validation will be essential to determine whether targeting SMAD4-dependent pathways can translate into meaningful clinical benefit. As systems biology continues to reshape cardiovascular medicine, SMAD4 exemplifies how proteomics can uncover nodal regulators that inform future precision cardiology strategies while highlighting the gap between molecular insight and clinical implementation.

FOOTNOTES

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