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Extracellular Vesicles in Vascular Calcification: Discoidin Domain Receptor-1 as a Novel Regulator of Fibrocalcific Response via Transforming Growth Factor-β Signaling

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Vascular calcification in the setting of atherosclerosis is a major determinant of morbidity and mortality in the Western world. Despite considerable advances in the field of cardiovascular medicine made in recent years, the growing need for effective therapeutic strategies to prevent and mitigate the process of plaque calcification, destabilization and rupture, leading to potentially lethal or debilitating cardiovascular events, remains largely unmet. Insights into the architecture of the calcified atheroma reveal a reciprocal interaction of fibrosis and calcification as a hallmark of its structural stability. In the thin fibrous cap of the vulnerable atherosclerotic plaque, microcalcifications formed by aggregation of calcification-competent extracellular vesicles exert mechanical stress on their surrounding matrix, thus facilitating rupture. The vascular cell-mediated fibrocalcific response is deemed a pivotal factor influencing plaque stability; however, the mechanisms and regulatory networks of extracellular vesicle-mediated fibrocalcific response in the context of vascular disease remain largely unknown.
This study aims to elucidate the regulatory mechanisms of calcific vesicle release in vascular fibrocalcific responses. As a result, the collagen receptor discoidin domain receptor-1 is introduced as a novel regulator of quantitative and qualitative extracellular vesicle release in vascular smooth muscle cells through the inverse regulation of two distinct transforming growth factor-β signaling pathways. Through discoidin domain receptor-1 response to extracellular collagen, upregulation of phosphorylated Smad3 and inverse suppression of phospho-p38 in vascular smooth muscle cells has an inhibitory effect on overt osteogenic differentiation, concomitant with a decrease in quantitative extracellular vesicle release, vesicle calcification potential and quantitative collagen synthesis.
The novel implication of discoidin domain receptor-1 as a regulator of fibrocalcific response identified in this study adds to a number of emerging mechanisms impacting on the process of calcific vesicle release and aggregation to form macro- or microcalcifications in the extracellular matrix, thus determining the vulnerability of atherosclerotic plaques. A systematic review of current literature juxtaposes vesicles implicated in physiological and pathological calcification processes and highlights several new players in the regulatory network governing osteogenic differentiation and calcific vesicle release by vessel wall-resident cells. Among these, the sorting protein sortilin, several members of the

annexin family, calcification inhibitors fetuin-A and matrix Gla protein as well as vesicle-dominant microRNAs were found to differentially influence osteogenic transformation and vesicle-mediated calcification potential. Consequently, these factors play a major role in determining the calcific phenotype of released extracellular vesicles conducive to ectopic cardiovascular mineralization.

In summary, the present work identifies discoidin domain receptor-1 and the transforming growth factor-β pathway as novel players in the regulatory network of atherogenesis. Furthermore, the study connects presently known regulators of vascular calcification to the processes of osteogenic transformation and release of calcification-competent extracellular vesicles in the setting of fibrocalcific response, determining pathological remodeling of the extracellular matrix. Continued studies may further our understanding of calcific plaque biology in order to identify potential targets for a new generation of anti-arteriosclerotic therapies. The present study forms yet another contribution to this cause, introducing discoidin domain receptor-1 and transforming growth factor-β signaling as novel regulators of vascular fibrocalcific remodeling in the vulnerable atherosclerotic plaque.