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Nuclear targeting apelin induces phenotypic transition of vascular smooth muscle cells

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Background: Apelin, and its receptor APJ, are a peptidic system playing a crucial role in vascular diseases. However, the role of apelin in atherogenesis and smooth muscle cell (SMC) proliferation remains unclear. We isolated 2 distinct SMC phenotypes from porcine coronary artery: spindle-shaped (S) and rhomboid (R). Biological features of R-SMCs (i.e. enhanced proliferative and migratory activities as well as poor level of differentiation) explain their capacity to accumulate into the intima. S100A4 is a marker of R-SMCs in vitro and of intimal SMCs, both in pig and human. S100A4 is a Ca2+-binding protein that can also be secreted; it has extracellular functions probably via the receptor for advanced glycation end products (RAGE).

Purpose: Investigate the effects of apelin on SMC phenotypic transition and S100A4 expression and release.

Methods and Results: We observed that apelin was highly expressed in R-SMCs particularly in their nucleus. P-SORT software analysis of preproapelin sequence suggested that N-terminal truncated apelin may target the nucleus, and we confirmed this in SMCs by overexpression of mutated preproapelin-His-tag. Transfection of mutated preproapelin-His-tag encoding plasmid in differentiated S-SMCs induced a transition towards a R-phenotype associated with increased proliferative activity, downregulation of SMC differentiation markers (i.e. alpha-smooth muscle actin), and increased nuclear expression and release of S100A4. In contrast, transfection of S-SMCs with wild type preproapelin-His-tag encoding plasmid did not induce nuclear targeting of Apelin or S100A4, and did not change the S-phenotype. Stimulation of S-SMCs with PDGF-BB, known to induce a transition to the R-phenotype, yielded nuclear targeting of both apelin and S100A4. In vivo, Apelin was expressed in SMC nuclei of stent-induced intimal thickening while its expression in the media was mainly cytoplasmic.

Conclusions: Our results suggest that nuclear targeting of apelin in SMCs acts on S100A4 expression and release, cell proliferation and differentiation. The pathophysiological consequences of this retargeting could be instrumental in the understanding of artherosclerosis.