Abstract:

S100A4, a key player in plaque stabilization?

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Topic(s): Atherosclerosis, Cerebrovascular Diseases, Aneurysm, Restenosis

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During atherosclerosis, intimal smooth muscle cells (SMCs) acquire a synthetic phenotype. We previously isolated spindle-shaped (S) and rhomboid (R) SMCs from porcine coronary artery. R-SMCs display the features of synthetic/dedifferentiated SMCs. S100A4 was identified as being a marker of R-SMCs in vitro and of intimal SMCs, in pig and man.

S-SMCs were treated with multimeric recombinant S100A4, which resulted in partial transition from S- to R-phenotype and NFκB activation. Remarkably, treatment of S-SMCs with multimeric S100A4 and platelet-derived growth factor-BB (PDGF-BB) together induced a complete SMC transition toward a R-phenotype associated with NFκB activation compared with multimeric S100A4 or PDGF-BB alone, likely through toll-like receptor-4 (TLR-4). RNA sequencing showed strong upregulation of pro-inflammatory genes such as granulocyte-macrophage colony stimulating factor (GM-CSF) and matrix-metalloproteinase-3 (MMP-3, Figure A) when cells were treated with multimeric S100A4 and PDGF-BB together compared with multimeric S100A4 or PDGF-BB alone.

In vivo, ApoE−/− mice were fed with high-cholesterol diet for 9 weeks. The 3 last weeks they were injected intraperitoneally with neutralizing monoclonal S100A4 antibody (clone 6B12, n=11) or with control IgG1 (n=12). Neutralization of extracellular S100A4 induced: decreased area of atherosclerotic lesions (Figure B), decreased necrotic core and cholesterol cleft, decreased number of CD68 positive cells and increased number of α-smooth muscle actin (Figure C) and smooth muscle myosin heavy chains-positive cells when compared to control groups.

Our results indicate that extracellular S100A4 could be a new target to influence the evolution of atherosclerotic plaque, leading to plaque stabilization.
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S100A4 and SMCs

A. RNA sequencing and real-time PCR showing GM-CSF and MMP-3 mRNA expression in S-SMCs treated with PDGF-BB, oligomeric S100A4 or both compared with control S-SMCs. **, p<0.01; ***, p<0.001. n=3 for each experiment. B. En face Oil red O staining and quantification of Oil red O positive area of thoracic-abdominal aorta from ApoE−/− mice treated with control IgG1 and anti-S100A4. (n=11 for anti-S100A4 and n=10 for control group). C. Representative double immunofluorescence staining for α-SMA and S100A4 of the aortic roots and quantification of α-SMA in intima from ApoE−/− mice treated with control IgG1 and anti-S100A4. Nuclei are stained with DAPI. (n=9 per group). Bar=200 μm.