Shear stress regulates endothelial autophagy: consequences on endothelial senescence and atherogenesis

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Atherosclerotic plaques form preferentially in arterial areas exposed to low shear stress (LSS) where endothelial cells express senescence-associated phenotypes. We tested the hypothesis that endothelial autophagy is an anti-senescence and anti-atherogenic process regulated by shear stress.

Endothelial cells exposure to LSS (2 dyn/cm², 24h) decreased LC3II/I ratio compared to high shear stress (HSS, 20 dyn/cm²)(1.6±0.2 vs. 2.0±0.3, respectively p<0.01). Bafilomycin A1 revealed that autophagic flux was elevated in HSS conditions. In mouse aorta, the surface of LC3 punctae/cell was lower in LSS than in HSS areas (9±1 vs. 15±1 mm²/cell, respectively p=0.01). Similar results were obtained in human carotid arteries. Both mTOR and AMPK pathways were involved in autophagy regulation by shear stress. Using culture endothelial cells, we observed more senescence-associated β-galactosidase activity under LSS than under HSS (48±3 vs. 37±3% positive cells, respectively p<0.05). Autophagy inhibition using wortmannin under HSS increased endothelial senescence when compared to vehicle (71±7% vs. 37±4% positive cells, respectively p<0.01), whereas autophagy activation using rapamycin under LSS prevented endothelial senescence (34±1 vs. 48±4% positive cells, respectively p<0.05). In vivo, endothelial senescence in HSS areas was higher in mice with an endothelial-specific deletion of Atg5 than in control mice, as evaluated by SA-β-gal staining (3.8±0.8 vs. 0.9±0.1 positive cells/mm², respectively p<0.01). No difference was observed in LSS areas. ApoE-/- mice with an endothelial specific deletion of Atg5 developed larger atherosclerotic lesions in HSS areas than control mice (3.1±0.5 vs. 1.4±0.4% respectively p<0.05), but no difference was observed in LSS areas.

In conclusion, endothelial autophagy is defective in endothelial cells in LSS areas and is associated with cellular senescence. This seems to contribute to the preferential development of atherosclerotic lesions in these areas.