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Bone morphogenic protein 4 regulates the shear stress-induced inflammatory pathway in aortic valve leaflets

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Objectives:

Pathologic hemodynamics has been shown to induce aortic valve (AV) inflammation and calcification. Although these processes are not completely characterized, it is hypothesized that inflammation occurs via a bone morphogenic protein (BMP) receptor-dependent pathway. This study aims at characterizing the inflammatory response of AV leaflets exposed to normal and altered shear stress conditions, and the potential role of BMP receptors.

Method:

The ventricular and aortic sides of AV leaflets were exposed for 48 hours to both pulsatile and oscillatory shear stresses *ex vivo* using three culture media: standard medium, osteogenesis-promoting medium, and standard medium supplemented with noggin (BMP antagonist). Immunohistochemistry was carried out to detect expressions of two well-known inflammatory markers VCAM-1 and ICAM-1, and the novel marker BMP-4.

Results:

Immunohistochemistry showed an increased inflammatory activity of the aortic surface exposed to pulsatile shear stress (altered hemodynamics) as compared to fresh tissue (four-fold increase in ICAM-1 and VCAM-1 expressions, six-fold increase in BMP-4 expression). The use of osteogenic medium under similar hemodynamics resulted in a eight-fold increase in BMP-4 expression as compared to fresh tissue. Finally, the use of noggin significantly reduced the inflammatory response observed with standard and osteogenic media.

Conclusions:

The results demonstrate that altered hemodynamics regulates the inflammatory response of AV leaflets. This response can be enhanced using an osteogenesis-promoting medium. The decreased inflammatory response observed using noggin is in agreement with cell studies and suggests that altered hemodynamics induces AV inflammation in a BMP-dependent manner.