Fountain of Youth in the Aorta
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Tales of longevity, eternal life and rejuvenation are everywhere in the world. This is, I think, partly because ageing is associated with a number of diseases, including cardiovascular, metabolic and neurological diseases. Discoveries of stem cells, including embryonic stem cells (ES cells) and induced pluripotent stem cells (iPS cells), have ignited an enthusiasm for regenerative medicine to repair the dysfunctional tissues or organs from such diseases. In a sense, these stem cells can be regarded as a modern form of the fountain of youth.

MSCs from Aorta    

Immune cells    

MMP-9    

Progression of AAA

MSCs from AAA

Figure. Mesenchymal stromal cells (MSCs) from a control aorta show the capacity to suppress immune cells. MSCs from AAA tissue show much weaker suppression of immune cells and secrete MMP-9, which may promote AAA progression. When cocultured, control MSCs can suppress MMP-9 secretion from AAA-MSCs. AAA, abdominal aortic aneurysm; MMP, matrix metalloproteinase.

control-MSCs suppressed the expression of MMP-9 by AAA-MSCs in a coculture experiment. The authors suggest that such an alteration of the immunomodulatory function of MSCs may be involved in AAA pathogenesis, and restoration of the immunomodulatory function of MSCs may be a promising therapeutic strategy.

This report by Ciavarella et al provokes a number of interesting questions and future research. I will discuss the nature of MSCs in the aorta, the immunomodulatory function of MSCs and the therapeutic potential of MSCs in AAA.

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better define MSCs, a phenotypic characterization has been proposed by the International Society for Cellular Therapy: positive for CD73, CD90, CD105 and negative for CD11b, CD14, CD34, CD45, CD79a and HLA-DR. The nature of MSCs derived from aortic tissue would be worth further investigation, including their molecular markers, self-renewability and differentiation capacity to make multiple lineages of cells. The difference between control-MSCs and AAA-MSCs is of interest. It is possible that control-MSCs and AAA-MSCs are entirely different populations. However, it is likely that they are similar, if not the same, populations because it is well established that the immunomodulatory function of MSCs is highly plastic in vitro. MSCs are usually suppressive to inflammation. However, when stimulated through pattern-recognition receptors such as the toll-like receptor (TLR) family, MSCs can be reprogrammed to express proinflammatory molecules. Thus, it has been proposed that MSCs can be dichotomized into proinflammatory MSC1 and anti-inflammatory MSC2, in an analogous way to M1 and M2 macrophages. As TLR signaling has been shown to participate in AAA pathogenesis, it is likely that MSCs in AAA tissue are reprogrammed to become the proinflammatory MSC1.

It is currently an open question whether the observed proinflammatory phenotype of MSCs in AAA is the cause or consequence of the inflammatory environment of AAA, or whether MSCs are involved in the pathogenesis of AAA. Apart from these questions, MSCs represent an attractive therapeutic target. Theoretically, exogenous MSCs can be used to ameliorate the inflammation in AAA by suppressing the infiltrating immune cells as well as the endogenous proinflammatory AAA-MSCs. Because cell-cell contact seems to be a prerequisite for the full activity of anti-inflammatory MSCs, delivery to the inflamed tissue would be essential for MSC-mediated therapy, which poses a serious challenge. Another attractive strategy is to reprogram endogenous AAA-MSCs to become anti-inflammatory MSC2, although reprogramming MSCs in vivo is another challenge. In this regard, it is noteworthy that coculture with control-MSCs suppressed the expression of MMP-9 by AAA-MSCs. It would be very interesting if suppression of MMP-9 is associated with the phenotypic change of AAA-MSCs toward the anti-inflammatory MSC2, which would provide conceptual evidence for the reprogrammability of AAA-MSCs.

Intensive research on AAA over the past decades has revealed that chronic inflammation plays a central role in its pathogenesis. The findings by Ciavarella et al provide another potential mechanism of the chronic inflammation in AAA involving MSCs. Hopefully we will some day be able to reprogram the proinflammatory MSCs in AAA tissue into the anti-inflammatory and tissue reparative MSCs that can rejuvenate the diseased aorta. Only future research will tell if we all have the fountain of youth in our aorta.

References