

Rejuvenating Senescent Mesenchymal Stem Cells: Implication for Vascular Tissue Engineering

The regenerative capacity of adult stem cells is known to decline with aging while aged stem cells enter a senescent state, which further impairs their function. Notably we recently discovered that ectopic expression of Nanog delayed senescence and restored the contractile function of adult ovine Mesenchymal Stem Cells (MSC). Here we report that Nanog does not only delay but can also reverse senescence of human MSC. In addition, we identified a novel mechanism through which Nanog restores the myogenic differentiation potential and contractile function of senescent MSC.

To study the effects of Nanog on senescent stem cells, tissue specific MSC such as hair follicle and bone marrow were isolated and transduced with a tetracycline regulatable vector that carries the Nanog gene. This system allows Nanog expression only when cells are treated with the tetracycline analogue, Doxycycline (Dox). To mimic stem cell senescence, cells were serially passaged until their proliferation capacity was seized (late passage, LP). Subsequently Dox was added to the culture medium and the stem cell myogenic capacity was evaluated and compared to early passage (EP) cells.

Our results show that senescent stem cells fail to respond to myogenic stimuli as evidenced by the loss of contractile proteins such as smooth muscle actin (ACTA2). In addition LP-MSC fail to polymerize ACTA2 into filaments and show decreased force generation capacity. Interestingly, Nanog expression in senescent MSCs restores the response to myogenic stimuli and induces ACTA2 expression, polymerization and force generation. Furthermore, we report that the loss of myogenic capacity in LP-MSCs is mediated through the decreased expression of critical myogenic transcription factors such as SRF. On the other hand, we show that Nanog restores myogenesis by reversing the loss of SRF and enhancing the transcriptional activity of the SRF DNA binding site (CArG box).

Taken together our data provide novel insight on the mechanism of stem cell senescence and propose a strategy to regain the lost properties, thereby increasing the potential of stem cells from aged donors for cellular therapy and tissue regeneration.

