

Endothelial Senescence in Skin Wound Repair

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Angiogenesis is required for organ regeneration and repair from injury. Cellular senescence, an irreversible cell-cycle arrest, is involved in age-related diseases, including cancer. However, cellular senescence is also required for tissue regeneration and repair; it has been reported that depletion of senescent cells inhibits wound repair. The role of endothelial cell (EC) senescence in angiogenesis and wound repair has not been examined before. When we create a dorsal wound in *C57BL/6* mice, the wound closes and blood vessel density increases 7 days after wounding. Expression of the senescent marker p16 is increased in ECs during wound healing in a mouse skin wound model. Bulk RNA-seq analysis of wounded skin reveals an increase in senescence genes during wound repair. Wound closure is significantly delayed, and blood vessel formation is inhibited in *p16-3MR* mice, in which p16⁺ senescent cells are depleted after ganciclovir treatment. Consistently, p16 knocked down ECs isolated from human subcutaneous tissues suppress vascular formation in the human EC organoid system. These results suggest that EC senescence is necessary for angiogenesis during wound repair.