

Abstract

The interaction of endothelial and perivascular cells is critical for the formation and stabilisation of the vasculature. In addition to their relevance for neoangiogenesis both cell types may promote mesenchymal tissue repair. However, the differentiation potential of endothelial and perivascular cells in skin wound healing is hardly characterised.

In this dissertation, the interaction of endothelial and perivascular cells to form a new vascular bed and their importance for mesenchymal tissue formation during cutaneous wound healing was studied. Initially, the distribution of vascular cells was defined by immunohistochemistry studies using the endothelium-specific protein PECAM1 and the perivascular cell-specific proteins desmin, α SMA and Sca1. Desmin⁺ or Sca1⁺ perivascular cells were closely attached to PECAM1⁺ endothelial cells within the dermal and hypodermal vasculature during the maturation of murine skin. Only few α SMA⁺ perivascular cells were detected within the vascular bed. In cutaneous wounds, PECAM1⁺ endothelial cells were re-distributed to form new vessels that were covered by desmin⁺ perivascular cells. α SMA⁺ and Sca1⁺ cells were found in the intervascular space on day seven and in close association to PECAM1⁺ vessels on day ten and day 14 post injury. Flow cytometry experiments revealed that in the intact skin and during wound healing Sca1 was also expressed by PECAM1⁺ endothelial cells. This PECAM1⁺/Sca1⁺ cell population was transiently increased at the peak of neoangiogenesis and myofibroblast formation, linking the PECAM1⁺/Sca1⁺ cell population to tissue repair. Sca1⁺ and PECAM1⁺ cells were not increased at this time point. In isolated PECAM1⁺/Sca1⁺ cells, the expression of endothelium- and perivascular cell-specific genes, e.g. *Pdgfrb* and *Tie2* as well as of the endothelial progenitor-specific gene *Cd34* was detected by RT-PCR. In addition, the cellular interaction partner of PECAM1, *Cd38*, was predominantly expressed in PECAM1⁺/Sca1⁺ cells. Sca1⁺ and PECAM1⁺ cells isolated from wounds started to express *Cd38* indicating that these cells acquire a PECAM1⁺/Sca1⁺/CD38⁺ phenotype. The cell surface localisation of TIE2, CD34 and CD38 proteins could be confirmed by flow cytometry analysis and association of CD38 to the vasculature was demonstrated by immunofluorescence microscopy. Cell-sorted wound-derived PECAM1⁺/Sca1⁺/CD38⁺ cells showed a superior differentiation into α SMA⁺ myofibroblasts *in vitro* when compared to Sca1⁺ perivascular and PECAM1⁺ endothelial cells. Ligation or ablation of the CD38 receptor *in vivo* resulted in an increased proportion of PECAM1⁺/Sca1⁺/CD38⁺ cells and α SMA⁺ myofibroblasts during wound healing. Hence, the

CD38 receptor signalling pathway may play an important role in regulating the activation of PECAM1⁺/Sca1⁺/CD38⁺ cells during tissue repair. In humans, a corresponding PECAM1⁺/CD38⁺ cell population was identified by flow cytometry and immunofluorescent analysis. This cell population was highly increased in biopsies of human basal cell carcinomas in areas of invading blood vessels.

In conclusion, endothelial and perivascular cells show an increased cellular plasticity in the adult mouse and human vasculature. Endothelial cells and perivascular cells may differentiate into PECAM1⁺/CD38⁺ cells during wound healing. This PECAM1⁺/CD38⁺ cell population provides a source of vascular cells, which can be activated by blocking the CD38 receptor signalling to promote neoangiogenesis and mesenchymal tissue repair. In basal cell carcinoma the CD38-dependent activation of the PECAM1⁺/CD38⁺ cell population may also regulate neoangiogenesis and thereby tumour growth.