SUMMARY

Fibroblasts are stromal cells ubiquitously present in the human body. They often appear in a quiescent state and can become activated in response to tissue remodeling signals. Activated fibroblasts acquire biosynthetic, pro-inflammatory and contractile properties, key functions for wound healing. In addition, the presence of permanently activated fibroblasts is one of the hallmarks of cancer. The purpose of this work is to investigate the differences between newborn and adult fibroblasts and keratinocytes in their implication in scarless wound healing, the origin of cancer associated fibroblasts (CAF)s and the influence of fibroblasts in melanoma invasion.

Evidence suggests that wounds heal almost without scar in newborns. To understand the mechanisms that contribute to scarless wound healing we focused on the differences between newborn and adult fibroblasts and keratinocytes, which are cells present in human skin and participating in wound healing process. A comparison of the expression profile between newborn and adult fibroblasts showed differentially regulated genes related to the acute phase of the inflammatory response and ECM organization, traits involved in wound healing. We also found that newborn fibroblast showed higher differentiation potential, exhibited markers of pluripotency and poor differentiation and expressed smooth muscle actin α (α-SMA) more frequently.

α-SMA expressing fibroblasts are called myofibroblasts and they are the main producers of ECM, and are key players in wound healing. Transforming growth factor beta (TGF-β) signaling pathway triggers the expression of α-SMA in fibroblasts. We noticed that newborn fibroblasts showed an upregulation of transcripts for TGF-β2 and TGF-β3, and downregulation of the transforming growth factor receptor II (TGF-R2) compared to adult fibroblasts.

In addition, the expression of α-SMA in both adult and newborn fibroblasts can be increased in coculture with newborn keratinocytes, indicating the importance of the crosstalk of fibroblasts with epithelial cells. The newborn keratinocytes showed expression of keratins (K)- 8, -14 and -19, markers of poor differentiation. This reminds the keratin expression profile of malignant cells.

In the second part of this work we examined the role of fibroblasts in melanoma invasion. We studied how the secretome from human fibroblasts and CAFs affected human melanoma cell line invasiveness in

vitro. Melanoma cells appeared more invasive when cultivated in conditioned media from CAFs. Cocultivation of CAFs with melanoma cells induced secretion of interleukin 6 (IL)-6 in fibroblasts and IL-8 in melanoma cells. High levels of IL-6 and IL-8 have been observed in melanoma patient serum. Moreover simultaneous blocking of IL-6 and IL-8 reversed fibroblasts induced melanoma cell invasiveness.

Since the source of CAFs is unclear we investigated the possibility that they can originate from cancer cells through epithelial-to-mesenchymal transition. For this purpose human cancer cells were grafted to nu/nu mice. Tumors were formed, they contained a well structured stroma containing typical smooth muscle actin cancer-associated fibroblasts. We observed that these cells did not originate from the xenografted cells, instead they were from the host origin.

Findings summarized in this thesis suggest that fibroblasts are a dynamic heterogeneous cells population and are key players in both wound healing and cancer.