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EDITORIAL

Editorial: Wound healing and fibrosis—two sides of the same coin

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"Truth is always strange, stranger than fiction" said Lord Byron. In the biological sciences, where some facts are believed to be truths, new findings often question what the truth "really" is. In the process in which data considered to represent the truth sink into oblivion, facts transit through a stage in which they can be described as half-truths: truth under questioning. In this issue of Cell and Tissue Research, we discuss current subjects related to the function of activated fibroblasts and the way that our perception of them is changing.

In recent years, it has become increasingly clear that the processes of wound healing and of tissue and tumour fibrosis display similarities at the molecular level (Rybinski et al. 2014; Zeltz and Gullberg 2016; Fig. 1).

That the soil, or local microenvironment, is important was noted as early as the late 1800s by Paget in classic work in which the importance of the "soil" for tumour growth and metastasis was suggested (Paget 1889). A century later, Dvorak observed that tumours are wounds that do not heal (Dvorak 1986). We have come a long way since then and now recognize that central, albeit ill-defined, cell types in these processes are the protomyofibroblasts and the myofibroblasts in the context of wound healing and tissue fibrosis, and the cancer-associated fibroblasts (CAFs) in tumours (Tomasek et al. 2002).

In the first part of the current issue, the role of the important matricellular protein periostin (Walker et al. 2016), which can act as an indirect link to the collagen matrices in granulation tissues, and the role of epithelial-to-mesenchymal transition in physiological and pathological wound healing processes will be discussed (Stone et al. 2016). Furthermore, the existence of multiple fibroblast populations in the skin and their role in the enigmatic phenomenon of scarless wound healing and the function of epidermal integrins in wound healing will be presented (Leavitt et al. 2016; DiPersio et al. 2016).

Often, fibrotically active fibroblasts are defined as cells staining positively for α-smooth muscle actin (αSMA) and the fibronectin splice variant EDA (FN EDA; Tomasek et al. 2002), a definition that now appears to be an overly broad generalization. A recent careful study tracing the fibroblast lineage has revealed that only 15% of the fibrotic fibroblasts are αSMA-positive in a heart fibrosis model (Moore-Morris et al. 2014). A recent publication has presented additional evidence, from multiple fibrosis models, supporting the idea that αSMA is an inconsistent marker for fibrotic cells (K.H. Sun et al. 2016). In the second part of the current issue, the origin of myofibroblasts and their role in fibrosis in the repair and remodeling of various tissues, such as heart and liver, will be discussed (Hutchenreuther and Leask 2016; Talman and Ruskoaho 2016; Lemoinne et al. 2016). Special emphasis will be placed on the integrin family and discoidin domain receptor family of cell-matrix receptors (Conroy et al. 2016; Coelho and McCulloch 2016) and on syndecans (Lunde et al. 2016). In addition, the role of hypoxia and of reactive oxygen species in tissue repair and fibrosis will be reviewed (Richter and Kietzmann 2016; Darby and Hewitson 2016).

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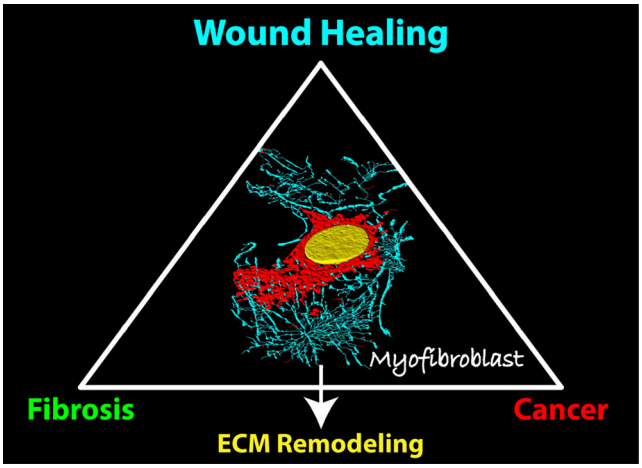

Fig. 1 Central role of myofibroblasts in wound healing, fibrosis and tumour-stroma interactions. The guest editors thank Dr. Heiti Paves, Universitiy of Tallin/Estonia, for providing images of myofibroblasts

Finally, in the last part of this special issue, some current themes relating to the tumour-microenvironment interface will be addressed. In the context of the tumour microenvironment, FN EDA is often claimed to be needed for myofibroblast activation. However, in some tumour models, it plays no role whatsoever (Astrof et al. 2004), and the possible role of FN EDA in myofibroblast activation might thus be highly context-dependent. Indeed, the expression of the FN EDA splice variant (whose FN-EDA-specific integrin-binding sites are cryptic; Kelsh et al. 2015; X. Sun et al. 2014) might be more of a descriptive biomarker for an activated fibroblastoid phenotype than a protein variant of functional importance for myofibroblast differentiation. Reviews in the last part of the issue will highlight the mechanisms of CAF activation (Kuzet and Gaggioli 2016), the roles of CAFs in therapeutic resistence (Mezawa and Orimo 2016), and the roles of TGF-β, shed syndecans and exosomes in tumour-stroma cross-talk (Piperigkou et al. 2016; Khan and Marshall 2016; Dhondt et al. 2016). Moreover, the properties of the tumour microenvironment in cutaneous squamous cell carcinoma will be discussed (Nissinen et al. 2016).

Taken as a whole, we believe that the current issue provides an excellent summary of the state of the art of the functions of connective tissue cells and their bidirectional interaction with the extracellular matrix in several fundamental biological processes that are related at the cellular and molecular level. In the years to come, the even better characterization of the cells that we call fibroblasts and the determination of the origin of the cells that we call myofibroblasts and CAFs will become crucial. New genetic tools such as lineage tracing are predicted to become increasingly important. Another central problem concerns fibroblast heterogeneity and the ability to distinguish between pro-fibrotic and anti-fibrotic fibroblasts and between tumour-supportive and tumour-repressive fibroblasts.

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