Wound healing disorders represent an important medical problem. This is particularly relevant for the elderly, who frequently suffer from complex disease states such as diabetes, venous stasis, or physical immobility, contributing to the development of chronic ulcers. In 1996, 6.5 million people in the U.S. suffered from skin ulcers, with the annual costs for diabetic ulcer treatment alone amounting to approximately $16-21 billion (1). These alarming numbers are likely to increase, taking into account the age distribution of the population in the Western world. In fact, an annual increase of 14% in the incidence of arterial/diabetic skin ulcers has been documented in the above report. Scarring is an equally important clinical problem, not only being associated with an unpleasant cosmetic appearance but often impairing skin function and growth.

Wound repair is the body’s response to injuries of the skin barrier, the main purposes being to secure the survival of the organism and to regain tissue function. These aims are achieved, in sequential stages, by terminating blood loss, preventing the entry of infectious microorganisms into the wound area, and restoring skin architecture (2). Clearly, the priorities assigned to these measures vary depending on the stage of life. In adult mammals, rapid wound closure and prevention of infection represent important goals of wound repair in order to guarantee survival. This is accomplished at the expense of incomplete tissue regeneration and scarring, often resulting in impaired tissue function. In contrast, in embryonal life, wound healing in a sterile, fluid environment does not require fibrin clot formation, and infection is less of a threat. Here, optimal tissue regeneration seems to have highest priority. This is consistent with the lack of significant inflammatory responses and the scar-free healing in embryonal wound repair (3).

The clinical significance of impaired wound healing and excessive scarring as well as the impact on society and health care systems are undisputed. The molecular and cellular basis of wound repair responses, however, is still not well understood. With the current theme issue “Wound Healing Mechanisms”, *Thrombosis and Haemostasis* aims to emphasize its new focus on wound healing research to expand this knowledge on basic cellular processes and mechanisms, thus helping to pave the way for novel therapeutic strategies to tackle wound healing disorders.

Wound repair is a complex physiological response requiring timely and precisely controlled cell-cell and cell-matrix interactions of circulating and resident cell types, as well as the activities of humoral tissue-derived components and blood elements (2). Circulating factors important for wound healing are for example sex hormones, in particular androgens, as reviewed by Gilliver et al. (4). Androgens most likely act on a variety of target cell types involved in all stages of wound healing. In contrast to the beneficial effects of estrogens, the overall effect of testosterone on wound repair appears to be detrimental. The outcome of wound repair is also determined by tissue-resident factors. This is illustrated in the review by Kyriakides and Bornstein on the functions of matricellular proteins in wound repair (5). Matricellular proteins are a group of proteins (including thrombospondin, SPARC, tenascin, and osteopontin), which regulate cell-matrix interactions rather than extracellular matrix structure and differentially modulate inflammation, angiogenesis, and tissue regeneration. Cell-matrix and cell-cell contacts are particularly important during wound contraction. Hinz and Gabbiani (6) outline in their article how myofibroblasts form structurally complex cell-matrix adhesions and cell-cell adherens junctions, which are specialized in developing and coordinating the tensile forces exerted on the wound granulation tissue.
The sequence of events involved in wound healing includes a number of cellular responses and regulatory mechanisms intimately related to vascular biology. This is documented by the fact that the first response to injury is the sealing of the wound by a thrombotic event. Platelet activation, adhesion and aggregation, and fibrin clot formation contribute to important functions of the haemostasis system and set the stage for later wound healing scenarios. Platelets contain and release a number of growth factors and chemokines (7), which regulate inflammatory responses and extracellular matrix production, vascular permeability and angiogenesis, and re-epithelialization. It can be hypothesized that platelet-derived growth factors modify the wound environment, e.g. by being deposited into the fibrin clot or into the extracellular matrix adjacent to the wound site. These growth factor reservoirs may facilitate local, short-term as well as long-term wound healing responses. In addition, the fibrin clot contains adhesion factors and serves as a provisional matrix for the migration of inflammatory, epithelial, or mesenchymal cells recruited into the wound area. For this reason, various types of fibrin sealants are being used in attempts to promote wound repair, as reviewed by Clark (8).

Nevertheless, re-epithelialization and overall healing are not impaired in fibrinogen-deficient or thrombocytopenic mice (9, 10). This finding demonstrates redundancy in the regulation of wound healing responses, possibly due to other cellular sources of growth factors and mechanisms of cell migration. Clot lysis is an essential event in wound repair as well. If fibrinolysis is impaired or lacking, fibrin strands formed in the wound area are insurmountable barriers for migrating keratinocytes, and re-epithelialization is completely arrested (11). Successful wound closure requires operative fibrinolysis that is initiated by two cooperating proteolytic enzyme systems, i.e. plasmin and metalloproteinases. Thus, understanding the orchestration of cellular and humoral haemostatic components together with tissue-specific events in wound healing responses will help to find solutions for various disease situations associated with wound healing problems.

References