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Preface

Wound healing and fibrosis – State of play

The multi-step repair process of wound healing displays one of the most complex biological events. In response to injury, the overlapping phases of haemostasis, inflammation, proliferation, extracellular matrix (ECM) formation, neovascularisation and tissue remodelling aim to restore tissue integrity and functionality. The highly dynamic healing process is orchestrated by various temporal and spatial regulators, such as growth factors, cytokines, matrix metalloproteinases, cellular receptors and ECM components [1,2]. However, pathological conditions can evoke excessive scarring and fibrosis, resulting in the formation of mechanically inferior scar tissue with disorganised ECM [3,4]. Chronic non-healing wounds, including diabetic wounds, fail to progress through the phases of wound healing in an orderly and timely manner, posing a persistent medical problem worldwide. Conventional treatment options mainly aim at wound closure rather than addressing the underlying pathophysiology, thus increasing healthcare costs and patient morbidity [5–7].

During evolution, the regenerative capacity of species appears to have gotten partially lost or diminished [8]. While still elevated at embryonic and neonatal stages, the ability to regenerate tissues in more evolved organisms, such as mammals, is restricted in adults, associated with scar tissue formation and fibrosis [3]. Protected from environmental disturbances and due to a variety of unique mechanisms operating during embryonic development, wound closure of embryos and foetuses follows regenerative processes, enabling healing in a scarless mode [9–11]. In order to recapitulate these events in the adult organism, we need to understand the underlying mechanisms of scarless healing down to the finest detail.

Another key aspect of efficient tissue growth and restoration is angiogenesis, the process of new blood vessel growth from pre-existing blood vessels [12]. Vascular perfusion is mandatory to sustain metabolic function for tissue maintenance, growth and repair [13,14]. This applies to highly vascularised tissues (e.g. skin, heart, liver, kidney), making induction and promotion of angiogenesis a promising target for effective treatment strategies. However, recent studies on avascular tissues (e.g. tendon, ligament, cartilage, cornea) suggest that as opposed to promoting angiogenesis during wound repair, limiting but not inhibiting neovessel formation may be beneficial for restoring tissue integrity and function [15–19]. As angiogenesis is a rate-limiting step for several pathologic conditions, anti-angiogenic therapies are already used in clinical practice to reduce cancer growth and, in ophthalmology, to prevent ocular neovascularisation in retinal diseases [20,21]. However, for attaining functional tissue regeneration by targeting angiogenic processes, we need a deeper understanding of the molecular and cellular mechanisms of physiological angiogenesis of the respective tissues.

This special issue comprehensively covers topics predominating issues and potential treatment strategies for wound healing and fibrosis with a focus on key regulators and fibrotic pathways [22,23]. In particular, the causes and potential novel treatment modalities of skin [24], muscle [25] and cardiac fibrosis [26] will be discussed. Approaches include tunable hyaluronan-based delivery systems [27], advanced therapeutic strategies targeting angiogenesis and tissue vascularisation in wound healing [28], local pharmacological induction of angiogenesis [29], matrix-assisted cell transplantation [30] and the potential benefits of limiting angiogenesis to modulate scar formation [31]. The collected work provides insight into the state-of-the-art and future perspectives of advanced drug delivery approaches for skin wound healing [32,33], bone tissue engineering [34] and intestinal inflammation [35]. Similarly, complications in diabetic wound healing [36] and failed repair mechanisms in articular cartilage [37] and intervertebral disc regeneration [38] are discussed. Finally, scarless wound healing [39] and skin re-epithelialisation [40] are highlighted as the ultimate goal in tissue regeneration and regenerative medicine.

An insufficient insight into the exact molecular mechanisms underlying impaired tissue repair is mirrored/reflected by the current lack of efficient therapies for functional tissue regeneration [41]. This underpins the need for the development of new therapeutic platforms that will address multiple pathophysiologic conditions to mediate healing in an active and physiologically relevant manner.

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Stefanie Korntner
Regenerative, Modular & Developmental Engineering Laboratory (REMODEL), Biomedical Sciences Building, National University of Ireland Galway (NUIG), Galway, Ireland
Science Foundation Ireland (SFI) Centre for Research in Medical Devices (CÚRAM), Biomedical Sciences Building, National University of Ireland Galway (NUIG), Galway, Ireland

Dimitrios I. Zeugolis
Regenerative, Modular & Developmental Engineering Laboratory (REMODEL), Biomedical Sciences Building, National University of Ireland Galway (NUIG), Galway, Ireland
Science Foundation Ireland (SFI) Centre for Research in Medical Devices (CÚRAM), Biomedical Sciences Building, National University of Ireland Galway (NUIG), Galway, Ireland
Corresponding author.
E-mail address: dimitrios.zeugolis@nuigalway.ie