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INTRODUCTORY ARTICLE

Inflammation, wound repair, and fibrosis: reassessing the spectrum of tissue injury and resolution

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Abstract

Estimates from various disease-specific registries suggest that chronic inflammatory and fibrotic disorders affect a large proportion of the world's population, yet therapies for these conditions are largely ineffective. Recent advances in our collective understanding of mechanisms underlying both physiological and pathological repair of tissue injury are informing new clinical approaches to deal with various human inflammatory and fibrotic diseases. This 2013 Annual Review Issue of *The Journal of Pathology* offers an up-to-date glimpse of ongoing research in the fields of inflammation, wound healing, and tissue fibrosis, and highlights novel pathways and mechanisms that may be exploited to provide newer, more effective treatments to patients worldwide suffering from these conditions.

Keywords: inflammation; fibrosis; wound healing

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Ever since the initial descriptions of the cardinal characteristics of inflammation – *rubor*, *dolor*, *calor*, and *tumour* – by the first-century Roman medical writer Aulus Cornelius Celsus [1], physicians and scientists have attempted to unravel the mysteries behind the human body's response to injury. Despite the fact that the basic steps underpinning the highly orchestrated and complex manner in which the body attempts to heal injuries (and it bears mentioning here that 'injury' is a term not limited solely to trauma, but also to the broader concept of disturbances in normal homeostasis due to infection, metabolic insults, degenerative or ageing disorders, malignant transformation ,and the like) are well known, we are still ignorant in key areas that may allow us to understand the fine-tuning of this response; hence, there is a strong need to periodically reflect on how far we've come in our knowledge and identify important gaps in evidence that require 'filling in'. For example, our abilities to predict when a wound will heal in a fashion that restores normal tissue homeostasis or will progress to a fibrotic, architecturally compromised tissue are limited. We do not yet fully comprehend why some fetal wounds heal without evidence of scarring, whereas others scar similarly to postnatal wounds [2]. Although tissue fibrosis clearly occurs following the resolution of inflammation, we do not yet understand why certain human diseases appear to result in scarring without significant antecedent inflammation [3]. Collectively, we appreciate that many malignancies share similarities with chronic inflammatory wounds [4] but it is only recently that we have begun to truly understand the role of host inflammatory and reparative cells in cancer development and progression. Similarly, we are becoming increasingly aware of the influence of non-cellular tissue constituents (extracellular matrix, soluble mediators, etc.) on tissue repair and homeostasis. These issues are not purely academic; recent estimates suggest that chronic inflammatory and fibrotic disorders are responsible for $142 billion in annual United States healthcare costs alone [5–7]. As a means to begin addressing some of these deficiencies (and many others) in knowledge, the 2013 Annual Review Issue on Inflammation, Wound Repair, and Fibrosis was born.

The highly interconnected nature of science creates significant artificiality in identifying discrete topics around which discussions of both physiological and pathological tissue repair revolve. By necessity, however, science is often performed in easily digestible 'bite-sized chunks' that allow us to answer specific questions using reductionist approaches and it is through this type of investigation that we hope to better understand the processes that define a physiological response to injury and the myriad ways in

which it can go awry. Perhaps the simplest (and most conventional) way to approach this topic is, as the title suggests, to divide the discussion among the concepts of inflammation (comprising the influx of inflammatory cells and mediators that orchestrate the initial response to tissue injury), wound healing (dealing with the physiological steps necessary to restore normal tissue structure and function), and fibrosis (concerning the pathophysiological response following injury that leads to ineffective and/or inappropriate tissue repair). To do so, however, invites the acknowledgement that the distinction between physiology and pathology is blurry, defined by matters of degree; enough inflammation and repair can heal a wound and restore tissue integrity and function, whereas excessive inflammation and/or repair (even if accomplished by physiological mechanisms) may lead to tissue dysfunction. Thus, while inflammation and fibrosis may occur due to abnormal processes, they may also be construed as 'too much of a good thing'. In this year's Annual Review Issue, we begin to tackle some of these issues, all the while recognizing that further work in these arenas will be necessary to advance our knowledge for purposes of appreciating the true underpinnings of tissue homeostasis, injury repair, and fibrosis.

Recognition of tissue injury and recruitment of inflammatory cells to sites of tissue injury is a fundamental aspect of cell biology and may occur via a number of very different mechanisms. For example, the innate immune system senses the presence of injurious stimuli through pattern recognition receptors; these receptors are critically attuned to the presence of exogenous pathogen-associated molecular patterns (PAMPs) and endogenous damage-associated molecular patterns (DAMPs), which largely comprise extracellular matrix (ECM) proteins, cell stress-induced proteins, and released immunomodulators [8]. Subsequently, recruitment and homing of inflammatory cells (primarily via chemokines and other cytokines) begins the process of controlling the injury and healing the tissue damage. Recent data suggest that the NLRP3 inflammasome, a key cellular sensor that results in the generation of an inflammatory response, is a critical component of the initial response to injury [9]. Moreover, tight regulation of chemokine expression and maintenance within tissues also directly influences the degree of inflammation, and evidence is emerging that an 'atypical' chemokine receptor (D6) plays an important role in this crucial aspect of tissue injury and inflammation [10]. Simultaneously (or shortly thereafter), mononuclear cell infiltration, to clear cellular debris and begin remodelling the injured tissues, occurs. It is noteworthy that all mononuclear inflammation is not the same; macrophage responses within injured tissues are quite plastic and are driven by the microenvironment, usually in preparation for resolving the inflammatory response via M2 polarization [11]. In the setting of chronic inflammation due to parasitic infection, the balance between M1 and M2 polarization is similarly accentuated and perhaps responsible for resolution of inflammation or the lack thereof [12]. It is also becoming clearer that fibroblasts, structural cells that participate in homeostatic regulation of tissue integrity, can be 'co-opted' by pathological processes such as malignancies to induce tissue injury and inflammation [13]. Whether this accumulation of fibroblasts in chronic malignant inflammation or fibrosis occurs due to enhanced proliferation or defects in autophagy (or both) is unclear, although evidence suggests that the balance between the two may be askew [14].

Several intracellular signalling pathways are emerging as potentially important for wound injury and repair, affecting cell fate and phenotype. To be sure, these pathways are also usually of significant import in health, where they maintain homeostasis and normal organ function. One such pathway, the Wnt/β-catenin pathway, has received a great deal of attention in this regard. Developmentally, Wnt9b and Wnt4 (ligands that activate the Wnt pathway) in the kidney provide impetus for mesenchymal-to-epithelial transition resulting in nephrogenesis. In damaged renal tissues, this pathway is re-activated as the kidney attempts to regenerate into functional tissue; however, in disorders of chronic injury and fibrosis, the regulation of Wnt may be dysregulated [15]. Similarly, reactive oxygen and nitrogen species, long known to induce tissue injury and contribute to disease pathogenesis, are also critical messengers of damage within tissues. Mechanisms to limit free radical generation or to scavenge/inhibit inappropriately-produced free radicals are important for cellular homeostasis, but evidence suggests that in the diabetic myocardium these adaptive measures may be abnormal, thereby promoting tissue injury [16]. Likewise, nitric oxide signalling and its attendant effects on vascular tone may play a role in wound healing, and experimental data suggest that dimethylarginine dimethylaminohydrolases influence wound healing in the lung to induce fibrosis [17]. Finally, recent attention has focused not only on *pro-inflammatory* mechanisms and mediators, but also on endogenous *anti-inflammatory* mechanisms that limit tissue inflammation and promote wound healing [18]. It warrants remembering that exuberant overexpression of anti-inflammatory molecules (eg TGF-β) promotes fibrosis and that limiting inflammation in disease may result in unintended consequences. Thus, the crux of research in this arena really should focus on how to resolve chronic inflammation without promoting tissue fibrosis – the Holy Grail.

Genetic and genomic variability likely accounts for some of the differences between individuals when it comes to the development of fibrosis or chronic inflammation, and both heritable and acquired traits have been implicated in wound healing and fibrogenesis. Epigenetic phenomena, including histone modifications and promoter hypermethylation, are known to influence gene expression in fibroblasts, macrophages, and other wound-healing cells. Moreover, evidence suggests that strategies to reverse these acquired DNA changes may have therapeutic benefit in fibrosis [19].

Along the same lines, investigation into a class of non-coding RNAs termed microRNAs (miRNAs) has only recently begun to elucidate their effects on gene expression. To that end, more than 1000 miRNA transcripts are known to be encoded by the human genome, and each one often controls a portfolio of genes. Evidence suggests that certain miRNAs may be instrumental in driving fibrogenesis, especially in light of miRNAs that affect TGF-β expression [20]. Within the nucleus, transcription factors also play a key role in driving cell phenotype and responses to external stimuli. While it is not uncommon for transcription factors to play multiple roles within cells, recent data have identified the early growth response-1 (Egr-1) transcription factor and its binding protein Nab2 in driving pathological fibrosis [21].

Increasingly, researchers in the fields of inflammation, wound healing, and fibrosis are recognizing that extracellular influences exist to alter the rate and efficacy of wound healing. For instance, it is becoming widely recognized that the ECM is much more than just scaffolding upon and in which cells reside, but rather a complex admixture of proteins that provide spatial and temporal context for cells. The importance of the ECM in directing such cellular functions is reflected in the recent coining of the term 'matrisome' to include ECM and ECM-related molecules that together direct cell function [22]. In fibrotic disorders, the ECM is typically produced by myofibroblasts (highly synthetic fibroblast-like cells with contractile capabilities) and may contribute significantly to tissue remodelling [23]. Similarly, empirical observations suggest that advanced age may have profound influences on inflammation and wound healing. As alluded to previously, fetal wounds are capable of healing without scar formation, although little is known about attendant mechanisms for this observation. In the human lung, ageing predisposes to fibrogenesis and this is explored in some detail [24]. Finally, emerging data suggest that the host itself is not the only source of influence on inflammation and wound healing. As discussed herein, the microbiome – the entire collection of organisms (bacterial, viral, fungal, etc.) inhabiting a host – also likely has a significant influence in host wound healing and fibrosis [25].

No scientific review on inflammation, wound healing, and fibrosis would be complete without providing examples of how our new-found knowledge will prove meaningful for patient care. With that in mind, Shechter and Schwartz explore the role of macrophages in central nervous system pathology (including psychiatric disorders) first by reviewing evidence that heterogeneity of cell sub-populations reveals destructive forces but also regenerative ones and then by positing how scientists may one day be able to harness salutary effects while inhibiting detrimental ones for purposes of therapeutic intervention in these difficult-to-treat disorders [26]. Similarly, Elnakish *et al*. critically appraise the role of stem cells of various origins in the development of experimental cardiac fibrosis and explore the possibility of cell-based therapy for patients with these disorders [27].

We have clearly come a long way since the four cardinal features of inflammation were defined. Yet we still have a way to go before we achieve clarity in understanding all the pieces that drive a successful inflammatory and wound healing response or promote a pathological fibrotic one. We hope that the articles in this Review Issue will enhance the reader's understanding, but also inspire further investigation that will ultimately improve the lives of our collective patients.

Author contribution statement

Both authors contributed equally to writing and editing the manuscript.

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