Seminars in Cell & Developmental Biology 20 (2009) 517–527

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Interrelation of immunity and tissue repair or regeneration

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ARTICLE INFO

Article history:
Available online 22 April 2009

Keywords:
Tissue injury
Wound healing
Regeneration
Inflammation
Immunity

ABSTRACT

Although tremendous progress has been achieved in understanding the molecular basis of tissue repair and regeneration in diverse model organisms, the tendency of mammals for imperfect healing and scarring rather than regeneration remains unexplained. Moreover, conditions of impaired wound healing, e.g. non-healing skin ulcers associated with diabetes mellitus or vascular disease, as well as excessive scarring, represent major clinical and socio-economical problems. The development of innovative strategies to improve tissue repair and regeneration is therefore an important task that requires a more thorough understanding of the underlying molecular and cellular mechanisms.

There is substantial evidence in different model organisms that the immune system is of primary importance in determining the quality of the repair response, including the extent of scarring, and the restoration of organ structure and function. Findings in diverse species support a correlation between the loss of regeneration capacity and maturation of immune competence. However, in recent years, there is increasing evidence on conditions where the immune response promotes repair and ensures local tissue protection. Hence, the relationship between repair and the immune response is complex and there is evidence for both negative and positive roles.

We present an overview on recent evidence that highlights the immune system to be key to efficient repair or its failure. First, we summarize studies in different model systems that reveal both promoting and impeding roles of the immune system on the regeneration and repair capacity. This part is followed by a delineation of diverse inflammatory cell types, selected peptide growth factors and their receptors as well as signaling pathways controlling inflammation during tissue repair. Finally, we report on new mechanistic insights on how these inflammatory pathways impair healing under pathological conditions and discuss therapeutic implications.

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doi:10.1016/j.semcdb.2009.04.009

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1. Introduction

1.1. Molecular and cellular principles of tissue repair

Restoration of tissue integrity and homeostasis following injury is a fundamental property of all organisms and there is a vast diversity among different organisms in how this process occurs. In mammalians the response to injury has been intensively studied over the past decades and in most organ systems the repair response requires a complex and dynamic interplay of numerous cell types, including tissue resident cells and hematopoetic cells recruited to the site of tissue damage, to accomplish the sequential stages of repair: inflammation, tissue formation and tissue maturation [1].

Tissue injury causes leakage of blood constituents into the wound site as well as release of vasoactive factors resulting in the activation of the clotting cascade. Clotted blood provides a matrix that determines cell adhesion and migration. Platelets trapped in the clot are important not only for hemostasis but also provide a source of growth factors and proinflammatory cytokines which mediate the recruitment of inflammatory cells and fibroblasts into the wound site. The *early inflammatory phase* of repair is characterized by local activation of the innate immune system, resulting in an early influx of polymorphonuclear leukocytes (neutrophils, PMN), followed by invasion of blood monocytes, which differentiate into tissue macrophages. Functional consequences of the innate immune response of the resident cells as well as the recruited inflammatory cells are not completely understood [2,3]. They combat invading microbes but may also critically support the repair process by releasing a spectrum of cytokines and growth factors, which initiate the phase of *tissue formation*. An imbalanced inflammatory response, on the other hand, may be detrimental to repair (Table 1). During the phase of tissue formation, newly formed granulation tissue, consisting of invading endothelial cells, macrophages and fibroblasts, covers and fills the wound area, followed by epithelialization to restore tissue integrity. Fibrin, fibronectin, vitronectin, tenascin are components of the provisional extracellular wound matrix which facilitate cell adhesion, migration and proliferation. At the wound edge, complex epidermal–mesenchymal interactions stimulate keratinocyte proliferation and migration [4]. Upon completion of epithelialization, cell proliferation and neovascularization cease, scar tissue forms and the wound enters the *maturation phase,* which lasts several months. During this last phase, a balance is reached between synthesis of new components of scar matrix and their degradation by proteases. The mechanisms determining granulation tissue regression and its transformation into scar tissue at the stage of tissue maturation are largely unknown. Typical features of these events include regression of vascular structures, transformation of fibroblasts into myofibroblasts, substitution of provisional extracellular matrix (ECM) by a permanent collagenous matrix and importantly resolution of the inflammatory response. Mechanisms that terminate the inflammatory response at the wound site are not well understood and may involve increased production of anti-inflammatory mediators, downregulation of proinflammatory factors, the normalization of microvascular permeability, induction of apoptosis of inflammatory cells and their efflux from the tissue.

Conditions of impaired wound healing, e.g. chronic skin ulcers associated with diabetes mellitus or vascular disease, as well as excessive scarring, represent major clinical and socio-economical problems. The development of innovative strategies to improve tissue repair and regeneration is therefore an important task that requires a more thorough understanding of the underlying molecular and cellular mechanisms. A cardinal feature of non-healing conditions and excessive scarring is an exaggerated and prolonged inflammatory response at the wound site (Table 1) [3,5]. The role that the inflammatory cells play in physiological and pathological tissue repair has, until today, not been clearly defined. The available data suggest that modulation of the local immune response may prove an effective therapeutic strategy in situations of impaired healing.

2. Mutual dependence of immunity and the repair or regeneration process

2.1. Evidence for inhibitory effects of the inflammatory response on regeneration and repair

Among the vertebrates, amphibians and fish are exceptional in their capacity to regenerate anatomically complete and fully functional tissues and organs at adult age. In particular, *urodele amphibians* (the newts and salamanders) can regenerate a diverse set of organs and tissues [reviewed in [6]]. The analysis of limb regeneration has received most attention, and much progress has been made to better understand its molecular basis. In urodele amphibians, regeneration involves dedifferentiation of cells at the site of amputation injury, followed by their proliferation to produce a blastema that finally reforms the missing tissue. The excellent capacity for regeneration may be related to the fact that the regenerative response induces only minimal inflammation in these species. However, to date few studies have addressed the interrelation of the immune response and limb regeneration in fish and amphibians.

Suggestive evidence for a negative role of the local inflammatory response on the regenerative capacity is derived from studies in anuran species, in particular *Xenopus laevis* [reviewed in [7,8]]. The gradual loss of the regenerative ability of developing tissues and the simultaneous maturation of the immune system as they approach and undergo metamorphosis (transition from larva to adult) is well documented. Hindlimb buds regenerate perfectly if partially removed at any time before metamorphosis. Amputation of developing hindlimbs at later stages results in increasingly deficient regeneration, manifested by production of smaller limbs with