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Review

Tissue-specific contribution of macrophages to wound healing

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ABSTRACT

Macrophages are present in all tissues, either as resident cells or monocyte-derived cells that infiltrate into tissues. The tissue site largely determines the phenotype of tissue-resident cells, which help to maintain tissue homeostasis and act as sentinels of injury. Both tissue resident and recruited macrophages make a substantial contribution to wound healing following injury. In this review, we evaluate how macrophages in two fundamentally distinct tissues, i.e. the lung and the skin, differentially contribute to the process of wound healing. We highlight the commonalities of macrophage functions during repair and contrast them with distinct, tissue-specific functions that macrophages fulfill during the different stages of wound healing.

Contents

1. Introduction

Wound healing is a highly dynamic and tightly coordinated process to achieve restoration of tissue integrity after infection or physical trauma. Fundamentally, this process can be divided into three overlapping but distinct phases. These phases have been defined as “coagulation and inflammation”, “tissue formation” and “tissue remodeling” [1]. During “coagulation and inflammation” the wound is provisionally closed by a blood clot and recruitment of inflammatory cells is initiated; during “tissue formation” pro-inflammatory signals decline and cell proliferation is initiated by local growth factors; and during “tissue remodeling” wound re-organization restructures the tissue [2] as shown for the skin in Fig. 1. Cells from the monocyte/macrophage lineage are critical players following tissue damage, and depletion of macrophages results in impaired wound healing [3–5]. In particular the capacity of myeloid cells to regulate inflammation, to remove apoptotic

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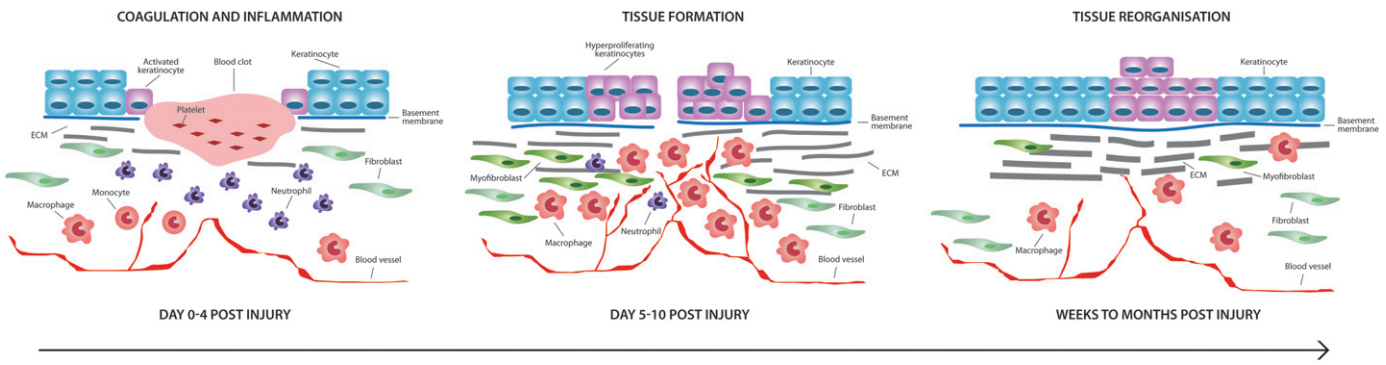

Fig. 1. Sequent phases of physiological skin wound healing.
During the "Coagulation and Inflammation" phase, immediately after injury, tissue-resident macrophages contribute to the initiation of a local inflammatory response, which leads to the influx of high numbers of neutrophils into the wound. In parallel, a fibrin clot forms, around which a provisional protective matrix is formed. During the "Tissue Formation" phase, a highly vascularized granulation tissue develops within the wound, comprising of a high cell density of mainly macrophages, fibroblasts and endothelial cells. Keratinocytes migrate from the wound margins to close the epidermal gap. During the "Tissue Reorganisation" phase, macrophages contribute to the active remodelling of the extra-cellular matrix within the wound, leaving behind a scar tissue that is characterized by increased matrix deposition and reduced cellular density.

cell debris and to promote cell proliferation have supported the notion that macrophages critically orchestrate the repair and healing response of damaged tissues [6]. Macrophages are present during all stages of the repair process and conditional depletion during the different phases of wound healing has revealed that macrophages fulfill distinct functional roles at the different stages, and emphasizes the great diversity and plasticity macrophages display during this process [7].

While many processes during wound repair are evolutionary conserved and follow similar mechanisms in different organisms and individual tissues, many other aspects of wound repair are regulated in a tissue specific context. Accordingly, tissue resident macrophage populations differ substantially from each other and may contribute to local wound healing in a tissue specific fashion. In this review, we compare the contribution of different macrophage populations to wound healing in two fundamentally distinct tissues, the skin and the lung. In this way, we separate common macrophage functions in wound healing from tissue-specific functions of macrophages, and review their distinct roles during the different phases of wound healing. Based on these different aspects, we propose a common model for the function of macrophages during wound healing.

2. Architecture and function of the skin

The skin forms a physical barrier between the organism and its environment, and thus a pivotal function of the skin is the protection from chemical and physical assaults, as well as from pathogen invasion and to prevent unregulated water loss [8]. Mammalian skin is composed of mainly two layers, the epidermis and the dermis, with a fat-rich subcutaneous tissue lying beneath the dermis (Fig. 2a). The epidermal layer is rich in cells and comprises a physical, chemical and immunological barrier, and the dermis, which is rich in extracellular matrix that provides tensile strength and elasticity. The epidermis is a squamous epithelium composed of different layers, supported by self-renewing proliferating tissue-stem cells within the basal layer [9]. The dermis is tightly connected to the epidermis by the basement membrane and consists of different

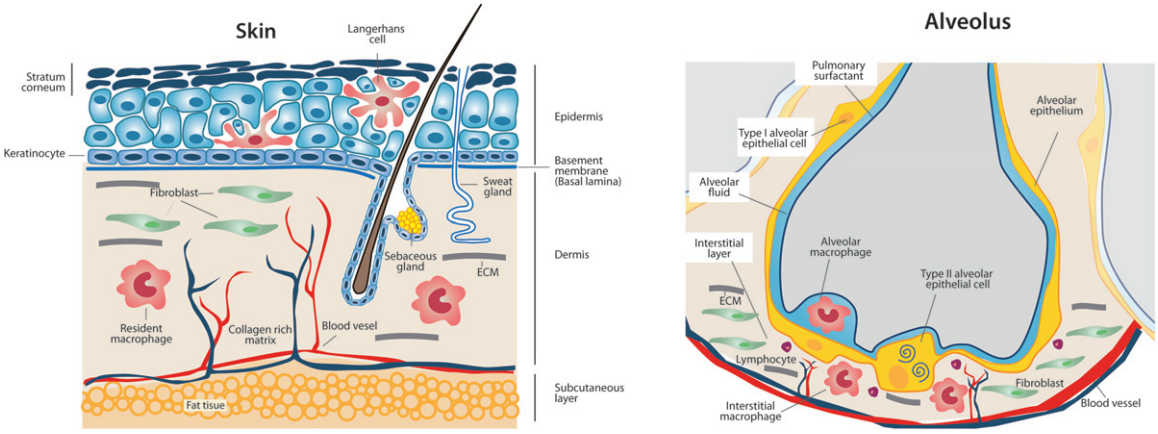

Fig. 2. Architecture of skin vs. alveoli.
The skin is composed of two layers: the epidermis and the dermis. The epidermis provides a physical, chemical and immunological barrier from the outside environment. The epidermis is a squamous epithelium composed of different layers, supported by self-renewing proliferating tissue-stem cells. In contrast, the dermis is a structure rich in extracellular matrix that provides tensile strength and elasticity. The dermis is tightly connected to the epidermis by the basement membrane and consists of different cell types, including fibroblasts and endothelial cells. Appendages such as hair roots, sebaceous glands and sweat glands are located in the dermal part. Langerhans cells are located in the epidermal layer whereas dermal macrophages are the dominant macrophage population in the dermal layer.
The pulmonary alveoli are the terminal ends of the respiratory tree forming an anatomical structure that allows for oxygen uptake. The alveolar sacs are composed of a thin alveolar epithelium composed of two cell types: thin, squamous type I cells, which cover 95% of the alveolar surface and form the structure of the alveolar wall, and cuboidal type II cells that secrete pulmonary surfactant. Surrounding the alveolar sacs, the lung interstitium is a connective tissue-rich framework for the alveoli and contains the interstitial macrophages. Lining the airway lumen alveolar macrophages are embedded in the alveolar fluid rich in pulmonary surfactants providing a barrier for lung defence.