Injury, Int. J. Care Injured 47 (2016) 2399–2406

Contents lists available at ScienceDirect

Injury

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

Review

The roles of immune cells in bone healing; what we know, do not know and future perspectives

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ARTICLE INFO

Keywords:
Bone healing
Bone fracture
Immune cells
MSCs

ABSTRACT

Key events occurring during the bone healing include well-orchestrated and complex interactions between immune cells, multipotential stromal cells (MSCs), osteoblasts and osteoclasts. Through three overlapping phases of this physiological process, innate and adaptive immune cells, cytokines and chemokines have a significant role to play. The aim of the escalating immune response is to achieve an osseous healing in the shortest time and with the least complications facilitating the restoration of function. The uninterrupted progression of these biological events in conjunction with a favourable mechanical environment (stable fracture fixation) remains the hallmark of successful fracture healing. When failure occurs, either the biological environment or the mechanical one could have been disrupted. Not infrequently both may be compromised. Consequently, regenerative treatments involving the use of bone autograft, allograft or synthetic matrices supplemented with MSCs are increasingly used. A better understanding of the bone biology and osteoimmunology can help to improve these evolving cell-therapy based strategies. Herein, an up to date status of the role of immune cells during the different phases of bone healing is presented. Additionally, the known and yet to know events about immune cell interactions with MSCs and osteoblasts and osteoclasts and the therapeutic implications are being discussed.

Contents

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http://dx.doi.org/10.1016/j.injury.2016.10.008
0020–1383/

Introduction

The interaction between bone cells, inflammatory mediators and constituents of the immune system involved in bone repair, continue to be of great scientific interest to researchers and clinicians [1–12]. Investigation of the critical role of immune cells during the bone healing is ongoing. Depletion of T- and B-lymphocytes is associated with impairment in bone mineralisation and maturation of osteoblasts with delayed repair and remodelling phases as demonstrated in experimental models [13,14]. Additionally, Cho et al. demonstrated that resident macrophages (osteal) are significantly involved in parathyroid hormone-dependent bone healing [15]. Although there are no experimental models for NK cell depletion in factures, an important role of NK cells during bone repair has been implied when a high level of interferon-gamma (IFN-γ) was detected in the diaphyseal regions of fractured femur in mice lacking T- and B-lymphocytes [16]. Conversely, as shown in immune-compromised animal model, bone marrow (BM) transplantation greatly enhanced the process of bone healing [17]. In addition to experimental findings, immune-compromised HIV patients can have delayed or non-union of fractures [18]. Thus, both animal and human studies confirmed the critical importance of innate and adaptive immune cells.

While the outer layer of cortical bone carries the weight bearing function, inner cancellous bone contains BM, a niche for different cell types including bone progenitor cells and multipotential stromal cells (MSCs). MSCs are classically identified as cells with the adherence capacity, which also express surface molecules CD90, CD73, CD105, but not hematopoietic lineage markers and are able to differentiate into bone, fat and cartilage cells [19]. Beside inflammatory cells and MSCs, two types of bone resident cells, osteoclasts and osteoblasts also play critical roles during the process of bone healing. Osteoclasts are large multinucleated cells are differentiated from monocyte lineage cells and have a bone degradation activity [20]. In contrast, the function of osteoblasts is the bone formation and they are derived from MSC-differentiated bone progenitor cells. Each of the immune cells has both distinctive and common functions with each other or MSCs during the phases of bone healing (Fig. 1). In this study, we review the vital role of the immune cells and their interactions with bone cells and MSCs (Fig. 2) and how this would affect the outcome of fracture healing.

Inflammatory phase

An early event of the injury of bone is the interruption of blood supply and platelet aggregation with the release of platelet-derived pro-inflammatory cytokines, Interlukin-6 (IL-6), Interlukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α). These cytokines stimulate the homing of lymphocytes and

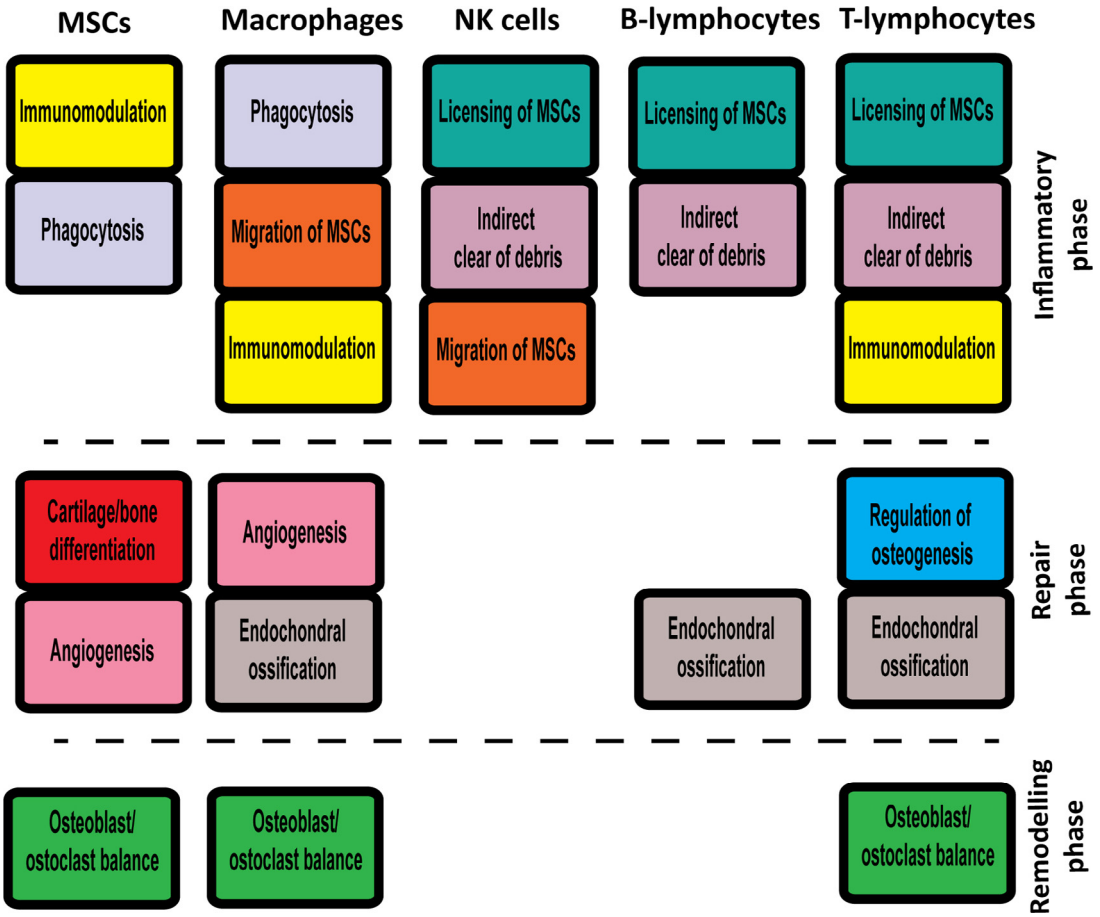

Fig. 1. The various roles of immune cells and MSCs during the phases of fracture healing. Early during inflammatory phase, both macrophages and MSCs can display phagocytic functions. NK cells, T- and B-lymphocytes are contributed into osteoclastogenesis to clear cell debris. The effects of macrophages and NK cells can facilitate the migration of MSCs. The licensing of MSCs can be mediated by cytokines released from NK cells, T- and B-lymphocytes. Then, licensed MSCs together with programmed macrophages and T reg lymphocytes have late immunosuppressive effects to end the inflammatory phase. During the repair phase, MSCs carry the differentiation functions as well as angiogenesis helped by macrophages. Also, T-lymphocytes are involved in regulation of MSC osteogenicity. The conversion of soft cartilaginous callus into hard callus is controlled by macrophages, T- and B-lymphocytes. In the final remodelling phase, osteoblast and osteoclast balance is regulated by MSCs and macrophages and probably T-lymphocytes (IL-17 and TNF-α effects).