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Review

Role of bone marrow macrophages in controlling homeostasis and repair in bone and bone marrow niches

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ABSTRACT

Macrophages, named for their phagocytic ability, participate in homeostasis, tissue regeneration and inflammatory responses. Bone and adjacent marrow contain multiple functionally unique resident tissue macrophage subsets which maintain and regulate anatomically distinct niche environments within these interconnected tissues. Three subsets of bone–bone marrow resident tissue macrophages have been characterised; erythroblastic island macrophages, haematopoietic stem cell niche macrophages and osteal macrophages. The role of these macrophages in controlling homeostasis and repair in bone and bone marrow niches is reviewed in detail.

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1. Introduction

1.1. Interdependence of bone and bone marrow

Bone marrow (BM), the principal haematopoietic organ in adults, is encased within bone, the primary function of which is to provide mechanical support and contribute to endocrine homeostasis. The bone is not just an inert site of residence for BM; they are interdependent organs that have reciprocal regulatory mechanisms throughout life [1]. Parallel functional decline in both systems is a major contributor to loss of productivity and well-being during aging [2] and disease [3,4]. Clear understanding of the cellular and molecular mechanisms responsible for the reciprocity is lacking. Herein we will discuss accumulating evidence suggesting that macrophages are a cellular link between these organs, focusing on macrophage contributions to haematopoietic systems within the BM as well as homeostasis and repair of bone.

1.2. Resident tissue macrophages

Macrophages, first described by Élie Metchnikoff, form a heterogeneous population of cells with diverse and adaptive transcriptomes [5,6]. All tissues of the body contain resident tissue macrophages, with hyaline cartilage being the possible exception. Resident tissue macrophages play significant roles in tissue/niche homeostasis, phagocytosis of cellular debris, tissue damage/injury repair, immune surveillance and inflammation resolution [7,8]. The mononuclear phagocyte system (MPS) was proposed to encompass this collection of functionally disparate but related cells. The MPS conceptualized that in postnatal tissues macrophages are continually replenished from blood monocytes derived from BM haematopoiesis [9,10]. Recent ontogeny studies have indicated that self-renewal of tissue macrophages also contributes to homeostasis [11–13]. Only one of these ontogeny studies has attempted to map BM macrophage origin [11] and showed that a subset of BM macrophages can self-repopulate while ontogeny of bone resident macrophages (osteal macrophages, osteomacs) has not been investigated.

1.3. Macrophages within the bone and marrow environment

BM topography is subtle and complex, involving an intricate patchwork of functionally designated microenvironments/niches [14]. The BM and bone contain multiple distinct resident macrophage populations that contribute to these specific niches and their specialised functions. The first recognised resident macrophages within BM stroma were the central macrophages within erythroblastic islands (erythroblastic island macrophages, EIM) [15]. A more recent discovery is the BM resident macrophage population involved in maintenance of hematopoietic stem cells (HSC) [16] that will be referred to here as HSC niche macrophages. Lastly, osteomacs, reside within the specialised tissues lining bone, including the endosteum which is continuous with adjacent BM [17]. See Fig. 1 for schematic representation of the confirmed macrophage subsets within bone and BM. Given the large number of functional niches within BM and bone, it is likely that new resident macrophage subsets will emerge.

1.4. In vivo *models of macrophage depletion*

In vivo mouse models of macrophage depletion have been used to study functional contributions of macrophages to erythropoiesis, HSC niches as well as bone homeostasis and repair. The Mafia (macrophage Fas induced apoptosis) transgenic mice contain a drug-inducible *Fas* suicide gene regulated by the *c-fms* promoter [16,18,19]. Inducible and efficient broad spectrum macrophage depletion is achieved in many tissues (significant reductions in F4/80$^+$ cells) [20] including BM macrophages [16,20,21] and osteomacs [18,21]. However depletion efficacy within specific BM macrophage subsets has not been explicitly reported and warrants more rigorous attention given recent improvements in subset phenotyping, as detailed below. Caution is needed when using the Mafia model as the transgene is also expressed by CD11b$^+$ myeloid cells including monocytes and myeloid precursors [16,20], osteoclasts [19], granulocytes [16,20] and dendritic cells [16,20,22]. Macrophage recovery occurs rapidly if depleting agent delivery is ceased [19,20].

Clodronate liposomes have been used extensively to deplete macrophages *in vivo* [23] including those in bone [18,19,21] and BM [16,24,25]. Internalisation of the clodronate-loaded liposome is required for apoptosis induction and consequently professional phagocytes are preferentially depleted in this model [23]. Consequently phagocytic potential of different macrophage subsets dictates depletion kinetics and sensitivity. For example, in BM EIM are particularly susceptible to clodronate liposomes [16], but granulocytes [16] and myeloid precursors are preserved. Both osteomacs and osteoclasts are efficiently depleted by clodronate liposomes [26]. An additional nuance of this model is that delivery route and delivery dose/regimen impact on the macrophage depletion specificity and sensitivity including target organ variation [21,23]. As discussed in detail below, both the Mafia model and clodronate liposome delivery induce HSC mobilisation, implying that both approaches target HSC niche macrophages.

The CD169-diphtheria toxin (DT) receptor (DTR) mouse is a more refined *in vivo* macrophage depletion tool [27]. It is a knock in model where human DTR cDNA has been recombined into the mouse CD169 gene. Thus DTR expression is regulated by the endogenous CD169 promoter. CD169 expression is restricted to a subset of tissue macrophages and is expressed by approximately 30% of BM F4/80$^+$ cells which includes HSC niche macrophages [28], EIM [24] and osteomacs [26]. This model avoids many undesired off-macrophage targets, including osteoclasts [26]. Other models of *in vivo* macrophage depletion have also been employed, but have yet to be rigorously characterised or broadly reproduced [29].

2. Macrophages and erythropoiesis

2.1. Role of EIM in regulating erythroblastic island niches

Erythroblastic islands comprise a central macrophage clustering numerous erythroblasts spanning the multistep erythroid maturation process (Fig. 1) [15]. EIM are essential for erythroblasts survival during their maturation to generate functional enucleated reticulocytes. The function of EIM, recently reviewed in detail [30], falls into three broad categories: a) secretion of trophic cytokines, b) iron transport [31], and c) phagocytosis and degradation of extruded nuclei [32,33]. BM macrophages can express erythropoietin (EPO) [34,35] the principal growth factor regulating erythropoiesis. Macrophages are also EPO responsive suggesting complex feedback loops may exist in response to EPO regulation of erythroid islands [36]. Macrophages can also express other factors that promote erythropoiesis including insulin-like growth factor-1[37,38] and bone morphogenetic protein (BMP) 4 [39], but direct confirmation of EIM expression and necessity for erythroid island integrity is lacking. Interestingly, all of the molecules have also been implicated in bone biology with dominant pro-anabolic effects [40–42] with the latter two also implicated in HSC homeostasis [43–45]. EIM also contribute to heme synthesis and iron recycling by incorporating iron into ferritin. The ferritin is then transported to erythroblasts for the synthesis of large amounts of hemoglobin [46]. Finally, through complex adhesion interactions the EIM aid