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Review

Digesting the role of bone marrow macrophages on hematopoiesis

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ABSTRACT

Tissue resident macrophages are found in various tissues like Langerhans cells in the skin or alveolar macrophages in the lung, and their main function is to regulate organ homeostasis. They have also been observed in the bone marrow and these cells in particular have been gaining importance in recent years as they are key players in hematopoiesis. However, as the characterization and classification of these putatively different bone marrow resident macrophages is far from established there is a need to generate an overview of tissue resident macrophages of the bone marrow. Here, we will review the current knowledge of bone marrow resident macrophages both in mouse and human. We will discuss the state of the art on the origin of bone marrow macrophages, specialized microenvironments where they reside and their unique characteristics. We will emphasize the two best studied examples of macrophage homeostatic function in the bone marrow, specifically within erythroblastic islands and the hematopoietic stem cell niche. Although increasing evidence shows that bone marrow resident macrophages are indispensable for hematopoietic stem cell function and bone marrow erythroid output, the field of bone marrow macrophages is in its infancy. This field is in dire need for a unified nomenclature to support functional experiments, model systems, and the identification of niches.

Contents

Abbreviations: BM, bone marrow; CAR cells, CXCL12-abundant reticular cells; DTX, diphtheria toxin; EMP, erythroblast macrophage protein; EMR, EGF-like module containing mucin-like hormone receptor; EPO, erythropoietin; G-CSF, granulocyte colony stimulating factor; HSC, hematopoietic stem cells; ICAM, intercellular adhesion molecule; ID2, inhibitor-of-differentiation 2; M1, classically activated macrophages; M2, alternatively activated macrophages; MerTK, MER proto-oncogene tyrosine kinase; MSC, mesenchymal stem cells; PBMC, peripheral blood mononuclear cells; PV, Polycythemia Vera; RANK, receptor activator of NF-κB; Rb, Retinoblastoma; TAM-receptor, TYRO3, AXL, MERTK receptor; VCAM, vascular cell adhesion molecule; VLA, very late antigen.

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1. Introduction

The bone marrow (BM) is a complex organ essential for the generation of all blood cells. It has been divided in various compartments, presumably dependent on the presence of different cell populations, secreted cytokines and chemokines. The definition of a niche was made in 1978 by Schofield where he described a niche as 'the stem cell is seen in association with other cells which determine its behavior' (Schofield, 1978). However, a broader definition precludes the necessity of stem cells and describes the niche as an array of different cell types in a specific location that is intradependent to elicit particular functions. In addition, there might be interdependencies between distinctive and comparable niches. Various macrophages have been identified in the BM, however, no ultimate panel of molecular markers for macrophages exists and thus it remains unclear if some macrophage populations are distinct or identical. Moreover, the tissue microenvironment may affect macrophage marker expression but not its functionality. Therefore, phagocytosis of expelled erythroid nuclei (pyrenocytes) in BM might be similarly regulated to phagocytosis of apoptotic cells at inflammatory foci in other tissues. Therefore, marker expression may not be the defining attribute to delineate specific macrophage populations but other parameters like the location within the tissue is of importance.

Macrophages are key regulators in both innate and adaptive immunity, however, they are also known for their role in tissue homeostasis, development and malignancy. Dependent on cues in the microenvironment, monocytic cells differentiate into macrophages with various phenotypes and functions, and they can be distributed to different tissues. In 2000, Mills et al. described a model for macrophage activation in which two major opposing macrophage activities were classified into subtypes: classical M1 or alternative M2 macrophages (Mills et al., 2000). M1 macrophages inhibit cell proliferation and induce a pro-inflammatory response, while M2 macrophages are anti-inflammatory, promote cell proliferation and are known to be involved in tissue repair and wound healing (Gordon, 2003; Goerdt et al., 1999; Ferrante and Leibovich, 2012; Martinez et al., 2008). The M1/M2 model has been used predominantly as it is a simple way to distinguish between the two functional properties of macrophages. However, it depicts M1 and M2 activation as clearly distinct processes, while macrophage polarization is naturally more complex (Martinez and Gordon, 2014). Therefore, the M2 population has been further divided into M2a-d macrophages based on inducing agents, marker expression and functionality irrespective of tissue residence (Martinez et al., 2009; Sironi et al., 2006; Roszer, 2015). This sub-classification becomes even more complex upon describing resident macrophages in different tissues as marker expression and functionality can be influenced by the specific niche in which these macrophages reside. This results in an array of different notifications and classifications for tissue resident macrophages making generalizations like the M2 sub-classification rather limited and oversimplified. In the following sections, we will therefore describe the different BM macrophages based on marker expression and functionality and will refrain from classical definitions like M1 and M2.

Within the BM, hematopoietic stem cell (HSC) homeostasis and erythropoiesis are controlled by macrophages. Osteal macrophages support HSC survival and retention in the BM and central macrophages are surrounded by erythroblasts to support erythropoiesis and osteal macrophage support. However, as the characterization and classification of these putatively different BM resident macrophages is far from established we recognize the need to generate an overview of tissue resident macrophages in the BM. Here, we will review the current knowledge of BM resident macrophages both in mouse and human. We will discuss the state of the art on the origin of BM macrophages, specific local microenvironments where they reside and their unique characteristics.

1.1. Origin of macrophages

Based on their origin, tissue resident macrophages can be divided into two subsets. One derives from the yolk sac and is maintained by self-renewal and proliferation. Another population originates from hematopoietic progenitors and circulating monocytes (Hashimoto et al., 2013). Until recently, it was believed that all macrophages including tissue resident macrophages derived from monocytes. However, the complicity and heterogeneity have been underestimated. In the last decade, interest has been grown to understand the development, relationship, function and origin of the different macrophage subsets within the different tissues, which has recently been appreciated to be partly dependent on the tissue niche in which these cells reside or home to. The present dogma, which came into existence during the 1960s and 1970s, is increasingly challenged. It dictates that tissue resident macrophages derive from *de novo* monocytes produced during myelopoiesis from definitive HSC in the BM. Monocytes may then home to their respective tissues and further differentiate into tissue resident macrophages or pro-inflammatory macrophages depending on the need (van Furth and Cohn, 1968; Virolainen, 1968; Morrison and Weissman, 1994). The general 20th century simplistic view of HSC differentiating to a common myeloid progenitor which further matures to a granulocyte-monocyte progenitor (GMP) and subsequently monocytes that exit the BM has gained in resolution with the discovery of a clonogenic progenitor (Lavin et al., 2015). This progenitor gives rise to monocytes, macrophages, and dendritic cells (Fogg et al., 2006), and more recently to a monocyte-restricted BM precursor termed common monocyte progenitor (cMOP) (Hettinger et al., 2013). Nevertheless, several lacunae concerning the presumed BM origin of tissue resident macrophages within this dogma remained.

At the start of the millennium several groups reported that recovery of specific tissue resident macrophages (*e.g.* microglia or Langerhans cells) after tissue damage did not involve donor cells but appeared to be of host origin (Hashimoto et al., 2013). Interestingly, monocytopenic mice present with normal macrophage distributions in the tissues (Kuziel et al., 1997). Several other authors showed persistent and maintained macrophage populations independent of monocyte production (Hoeffel et al., 2015; Lavin et al., 2014). These results suggested that certain macrophage populations do not arise from BM monocytes. Further investigation using parabiotic mice, selective ablation using specific macrophage markers, gene expression analysis and single population tracing led to the notion that a selection of tissue macrophages are derived independently from BM myelopoiesis (Hashimoto et al., 2013). Surprisingly, these cells are able to undergo renewal divisions in order to repopulate the tissue after injury or insult to the tissue. Phenotypically these cells are completely different from the inflammatory macrophage (Martinez and Gordon, 2014). Interestingly, host-derived recovery of macrophages in specific tissues after whole body irradiation prior to BM transplantations of mice can arise independently which suggests the presence of BM myelopoiesis independent macrophages. The origin of these specific macrophages, their renewal capacity, signaling cues that maintain these cells and whether tissue resident effector cells and renewal populations are different entities are currently vividly pursuit within the field. Recently, it has been shown that minor populations of macrophages in specific tissues are originating from yolk sac myelopoiesis and derive prior to the establishment of definitive HSC dependent hematopoiesis (Hashimoto et al., 2013) It suggests that a selection of macrophages find their origin in early embryogenesis and maintain their tissue presence, function-