Immunobiology 220 (2015) 169–174

Contents lists available at ScienceDirect

Immunobiology

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

Review

Self-renewing macrophages – A new line of enquiries in mononuclear phagocytes

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ARTICLE INFO

Article history:
Received 17 May 2014
Received in revised form 3 November 2014
Accepted 5 November 2014
Available online 11 November 2014

Keywords:
Embryonic
GM-CSF
Heterogeneity
M-CSF
Macrophage
MPI cells
Self-renewal

ABSTRACT

Mononuclear phagocytes have been viewed for a long time as one distinct lineage where continuous division of haematopoietic progenitor cells give rise to and replenish differentiated mature cells with a limited life-span. Very recent data have demonstrated however, that in addition to this, proliferation of differentiated macrophages of mostly embryonic origin also contribute significantly to the mononuclear phagocyte system. Recently developed primary tissue culture models of self-renewing differentiated resident macrophages are now available to facilitate our understanding of macrophage heterogeneity and to provide special tools to study general and specific macrophage functions as well. In this review, we will focus on current knowledge on the concept of self-renewing macrophages and discuss aspects of their origin, development and function.

Contents

Introduction

Macrophages are cells playing crucial roles in various diseases and also in normal tissue homeostasis. They are capable of phagocytosis, this "ancient" ability to engulf particles resembles single-cell eukaryotic organisms (Siddiqui and Khan, 2012). This property puts them into the first line of defence against invading infectious pathogens. Phagocytosis is also important in

Abbreviations: MPS, mononuclear phagocyte system; HSCs, hematopoietic stem cells; GM-CSF, granulocyte macrophage colony-stimulating factor; M-CSF, macrophage colony-stimulating factor; IL-4, interleukin-4; IL-13, interleukin-13; DCs, dendritic cells; LPS, lipopolysaccharide; BMMs, bone marrow derived macrophages; MPI, Max Planck Institute; TNFα-, tumour necrosis factor α.

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http://dx.doi.org/10.1016/j.imbio.2014.11.005
0171-2985/

other roles of macrophages such as tissue redistribution during development or in pathologic conditions such as wound healing and cancer (Biswas et al., 2012). These vastly diverse functions explain that macrophages constitute a very heterogeneous group of cells expressing characteristic and distinct surface markers and exhibiting distinct biological properties. Compared to other cells of the body, macrophages are the cells expressing most of the pathogen associated molecular pattern (PAMP) and danger associated molecular pattern (DAMP) recognizing receptors; however, there is significant variability for the levels of these receptors within macrophage subsets which is also reflected in the induced gene expression responses (Zarember and Godowski, 2002; Kumar et al., 2011). Thus, it is very important to delineate mechanisms and functional differences involved in this cellular heterogeneity as this may enable us to comprehend and influence specialized macrophage functions in various disease states. To this, understanding of the newly emerged concept of self-renewing macrophages can contribute significantly.

Self-renewing macrophages under homeostatic conditions

The mononuclear phagocyte system

Until recently, heterogeneity in the macrophage system in various tissues in vertebrates has been explained almost exclusively by the effect of the local milieu on differentiating macrophages at different anatomical locations (Geissmann et al., 2010). In the late sixties, the idea of the mononuclear phagocyte system (MPS) has been proposed (Langevoort et al., 1970; van Furth and Cohn, 1968). In this model, tissue macrophages originate from self-renewing multipotent haematopoietic stem cells (HSCs) that multiply in the bone marrow and produce blood monocytes. These cells do not divide further but colonize certain tissues where they differentiate into the various types of macrophages. This diversification process is driven by tissue specific cell to cell contacts and by locally produced soluble factors (Van Furth et al., 1972). This model of tissue macrophage production and maintenance corresponds to general models of cell differentiation that is experienced in various tissues in adult vertebrates (*e.g.* liver, skin, intestine), where cell multiplication is only associated with progenitor stem cells but not with differentiated cell types (Morrison et al., 1997). This model of the MPS was supported by radiolabelling studies and also by the demonstration that bone marrow transplantation leads to the appearance of macrophages of donor origin in peripheral tissues (Godleski and Brain, 1972; Gale et al., 1978). The dominance of this linear model was widely accepted even though exceptions to this rule, such as the demonstration of resident macrophage multiplication in various organs under homeostatic conditions or upon bone marrow or blood monocyte depletion has been demonstrated (Sawyer et al., 1982; Yamada et al., 1990; Van Furth and Diesselhoff-den Dulk, 1984; Tarling and Coggle, 1982).

Self-renewal of tissue resident macrophages

In time, overwhelming evidence accumulated that the bone marrow derived MPS is not an exclusive system of mononuclear phagocytes. The presence of macrophages has been shown in the developing embryo before the presence of HSCs (Lichanska et al., 1999; Shepard and Zon, 2000). This indicated that macrophages are not originating from a single lineage. The first differentiated macrophage cell type for which a definitive proof of self-renewal in adulthood has been established was the microglia (Priller et al., 2001). The origin of these cells has been shown to be embryonic, as their progenitors come from the yolk sac. Furthermore, some of these differentiated cells have been shown to persist and self-renew. Nevertheless, embryonic macrophages are not the exclusive source of microglia as a subpopulation of these cells originates from the bone marrow (Simard and Rivest, 2004). Langerhans cells, the macrophages of the epidermis, have been shown to self-renew, both in humans and in mice (Merad et al., 2008) and, similarly to microglia their dual (embryonic and adult bone marrow) origin has also been demonstrated (Ginhoux et al., 2006; Chorro et al., 2009). A possible negative effect of the MafB and cMaf transcription factors on macrophage self-renewal has been suggested using gene knockout mice. In the absence of these proteins both monocytes and various differentiated tissue macrophages (such as Kupffer cells and splenic macrophages) multiply in response to high concentrations of M-CSF *in vitro* (Aziz et al., 2009). These cells are not transformed and remain functionally intact. The functional consequence of the deletion of MafB and cMaf appeared to be the elevation of Myc and Klf4 protein levels and suggested a general role for Myc and Klf4 in resident macrophage multiplication.

Multiple lineages of self-renewing tissue resident naïve macrophages

As the methodology of developmental biology advanced, it became evident that not only microglia, but several other types of macrophages in different tissues of adult mice derive from yolk-sac macrophages (Schulz et al., 2012). These cells can be found in various organs and show a characteristic phenotype: they strongly express the F4/80 antigen, are independent of the Myb transcription factor and possess a typical pattern of gene expression. Although these F4/80^{hi} cells persist in adult organs it was not clear if self-renewal or longevity is the dominant mechanism for their continuous presence.

More recent genetic fate-mapping and parabiosis experiments led to an even more drastic change in the understanding of tissue macrophage origins. These studies demonstrated that in naïve mice F4/80^{hi} organ macrophages derive almost exclusively from embryonic progenitors and in most cases local self-renewal is responsible for their maintenance (Hashimoto et al., 2013; Yona et al., 2013). A significant exception to this rule are intestinal macrophages that originate from the bone marrow and are constantly replenished by incoming blood monocytes (Yona et al., 2013; Bain et al., 2013). Fig. 1 depicts the origins of tissue macrophages.

Self-renewing macrophages during inflammation

A significant part of inflammatory macrophages derive from bone marrow derived blood monocytes recruited to the site of injury. Many of these cells have a short half-life and do not multiply. Interestingly, self-renewal can contribute to increased numbers of inflammatory macrophages as well. Both embryonic derived resident macrophages and bone marrow/monocyte derived cells have been shown to self-renew during helminthiasis or in response to recombinant IL-4 (Jenkins et al., 2011, 2013) and also in zymosan or thioglycollate elicited peritonitis models (Davies et al., 2013).