Cellular Immunology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Cellular Immunology

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

Research paper

# Niche signals and transcription factors involved in tissue-resident macrophage development

Wouter T'Jonck*, Martin Guilliams, Johnny Bonnardel*

*Laboratory of Myeloid Cell Ontogeny and Functional Specialization, VIB-UGent Center for Inflammation Research, Technologiepark 927, 9052 Gent, Belgium*
*Department of Biomedical Molecular Biology, Ghent University, Technologiepark 927, 9052 Gent, Belgium*

ARTICLE INFO

*Keywords:*
Developmental immunology
Macrophage development
Niche
Tissue-resident macrophage
Transcription factors

ABSTRACT

Tissue-resident macrophages form an essential part of the first line of defense in all tissues of the body. Next to their immunological role, they play an important role in maintaining tissue homeostasis. Recently, it was shown that they are primarily of embryonic origin. During embryogenesis, precursors originating in the yolk sac and fetal liver colonize the embryonal tissues where they develop into mature tissue-resident macrophages. Their development is governed by two distinct sets of transcription factors. First, in the pre-macrophage stage, a core macrophage program is established by lineage-determining transcription factors. Under the influence of tissue-specific signals, this core program is refined by signal-dependent transcription factors. This nurturing by the niche allows the macrophages to perform tissue-specific functions. In the last 15 years, some of these niche signals and transcription factors have been identified. However, detailed insight in the exact mechanism of development is still lacking.

## 1. Introduction

Tissue-resident macrophages were first described by the Russian scientist Élie Metchnikoff in 1883 [1]. These cells are present in all tissues of the body where they form a first line of defense against pathogens and play an essential role in maintaining tissue homeostasis [2,3]. In the past decade, new insights have been gained in the origin of tissue-resident macrophages. Briefly, they are derived from three progenitors, being yolk sac macrophages, fetal liver monocytes and circulating monocytes, which colonize the tissues in consecutive waves (Reviewed in [4,5]).

Tissue-resident macrophages share several common features such as the ability to phagocytize particles, pathogens and dying cells, initiate immune responses through the production of cytokines and chemokines and the expression of markers such as CD11b, F4/80 and CD64 which are often found on the cell surface of murine tissue-resident macrophages [6–10]. These features are part of a core macrophage program which is largely shared by all tissue-resident macrophages. Next to these common features, each macrophage population has a unique identity and function. Interestingly, this functional specialization is dependent on the tissue in which they reside. For example, it has been shown recently that cardiac macrophages facilitate electrical conduction through Cx43-containing gap junctions with cardiomyocytes [11]. By contrast, tissue-resident macrophages located in the brain, called microglia, are small star-shaped cells with an extensive lamellipodial network and while they are involved in brain surveillance by constantly probing the cellular environment, they are also crucial for brain development and homeostasis by regulating the synaptic pruning during postnatal development [12–14]. Another example are the lung alveolar macrophages which are involved in the clearance of alveolar surfactant [15]. The tissue-specific function of these macrophages implies that they must have a different functional identity. This functional specialization is governed by tissue-specific signals which regulate the expression or activity of signal-dependent transcription factors (TFs). In turn, these TFs adapt the core macrophage program by activating functional modules, which gives macrophages their functional identity.

In this review, we will first briefly touch upon the major lineage-determining TFs that establish the core macrophage program. Second, we will discuss the signal-dependent TFs which adapt this core program in response to environmental cues, allowing macrophage to perform tissue-specific functions.

## 2. Lineage-determining transcription factors and the core macrophage program

Macrophages form a very diverse group of mononuclear phagocytes. Despite this heterogeneity, a large transcriptional network and

*Abbreviations:* CNS, central nervous system; DC, dendritic cell; KO, knockout; LC, Langerhans cell; NE, norepinephrine; OPG, osteoprotegerin; TF, transcription factor

* Corresponding authors at: Technologiepark 927, B-9052 Ghent (Zwijnaarde), Belgium.
*E-mail addresses:* Wouter.tjonck@irc.ugent.be (W. T'Jonck), Johnny.bonnardel@irc.ugent.be (J. Bonnardel).

https://doi.org/10.1016/j.cellimm.2018.02.005
Received 10 November 2017; Received in revised form 7 February 2018; Accepted 10 February 2018
0008-8749/ © 2018 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/BY/4.0/).

epigenetic landscape is shared among all macrophage populations [16–18]. This core macrophage program is established by a group of lineage-determining TFs which perform a general role in myelomonocytic development by determining stem cell fate.

One of the most well studied master regulators in macrophage development is PU.1, which is regulated by RUNX1 (also known as AML1) [19,20]. During the early stages of myeloid cell development, PU.1 determines myeloid progenitor fate in a concentration-dependent manner. A high amount of PU.1 leads to the development of macrophages whereas a low level of PU.1 is necessary for B cell development [21]. This concentration-dependent effect can be attributed to the numerous low- and high-affinity PU.1 binding sites present in the genome [22]. The low-affinity binding sites are only bound by PU.1 when a certain threshold concentration is exceeded. The developmental role of PU.1 is not restricted to macrophages and B cells. For example, PU.1 also regulates dendritic cell (DC) development in a concentration dependent manner through regulation of *Flt3* expression [23]. One of the major target genes of PU.1 in macrophage development is *Csf1r* [20], which encodes the receptor for interleukin-34 (IL-34) and monocyte colony-stimulating factor (M-CSF). IL-34 is specifically required for the development and maintenance of microglia and Langerhans cells [24,25], whereas M-CSF is involved in survival, proliferation and maintenance of most other mononuclear phagocytes [26]. Together, PU.1 and *Csf1r* are essential for the formation of yolk sac macrophages [27]. Generally, PU.1 is involved in tissue-resident macrophage development by acting as a scaffold for histone modifiers which establish an enhancer landscape [28]. In addition, many TFs involved in tissue-resident macrophage development, function and activation perform their function through interaction with PU.1. For instance, it was shown that c-Jun can enhance the ability of PU.1 to drive expression of M-CSFR [29]. In addition, *Zeb2* has been recently described as being involved in M-CSFR regulation in the bone marrow [30] and has been proposed to be part of the core macrophage program since it is expressed in pre-macrophages, but this still remains to be validated [16].

Upon terminal differentiation, MafB is expressed by tissue-resident macrophages causing them to exit the cell cycle [31]. MafB, together with c-Maf, desensitize macrophages from the proliferative effect of M-CSF by inhibiting the expression of self-renewal genes such as *Myc*, *Klf2* and *Klf4* [32]. This happens through direct inhibition of macrophage enhancers, including PU.1. In self-maintaining tissue-resident macrophage populations, the inhibition of these enhancers can be temporarily lifted, allowing differentiated tissue-resident macrophages to re-enter the cell cycle [32]. Contrary to regenerative processes, this is not accompanied by dedifferentiation of the tissue-resident macrophages [31,33]. In addition, MafB is essential for F4/80 maturation [34] and is involved in actin remodeling [35].

Other lineage-determining TFs have been proposed, including *Batf3*, *Pparg*, *Irf8* [16]. It is however not clear whether these factors are strictly needed for macrophage development. Moreover, it is unknown whether macrophages require continuous expression of these factors for their maintenance, survival or function.

Together, these lineage-determining TFs establish the core macrophage program during the pre-macrophage stage. This core program includes *Cx3cr1*, pattern recognition receptors, phagocytic receptors, Fcγ receptors (e.g. *Fcgr1*, encoding CD64), *Sirpα*, *Iba1*, *Mertk* and *Adgre1* (F4/80) which are expressed by almost all macrophage populations [7,16,36,37]. Additionally, these lineage-determining TFs shape the epigenome and form an anchor point for signal-dependent TFs.

## 3. Niche signals and signal-dependent transcription factors

Despite many similarities, macrophage identity and function are very diverse and unique for each tissue [6]. This implies that the core macrophage program, established during early development, has to be adapted in a tissue-dependent manner. According to the niche hypothesis [38], each macrophage is located in a particular niche which offers physical support and nurtures the cell through production of niche signals. These niche signals may include cytokines, metabolites and cell-cell contacts which initiate tissue-specific transcriptional networks in the pre-macrophages upon engraftment by driving signal-dependent TF expression or activation [39]. These signal-dependent TFs work in concert with lineage-determining TFs to refine the core macrophage program and imprint a transcriptional program in the tissue-resident macrophage to meet tissue-specific needs. This is done through direct activation of signature genes or by inducing chromatin remodeling which enables signal-dependent TFs to active signature genes [17,18,37,39]. These signature genes are often required for the functional maturation and/or survival of tissue-resident macrophages. In this section, we will give an overview of the niche signals and their corresponding signal-dependent TFs in different macrophage populations (Fig. 1).

### 3.1. Red pulp macrophages

The spleen contains multiple subsets of macrophages, among them red pulp macrophages located in the red pulp of the spleen. They play a vital role in the clearance of senescent red blood cells, induction of regulatory T cell differentiation and protection against parasites through production of type I interferon [40–44]. Many advances have been made on signal-dependent TFs regulating the differentiation of these macrophages, among them the discovery of the essential role of SPIC in their development.

SPIC is a PU.1-related transcription factor which is highly expressed by red pulp macrophages, bone marrow macrophages and part of the F4/80$^{hi}$ liver macrophages [41,45]. Kohyama et al. have shown that *Spic*$^{-/-}$ mice have a cell-autonomous defect in the development of red pulp macrophages that can be reverted by retroviral SPIC expression in bone marrow cells [41]. Of note, no defects were observed in monocytes or other macrophage populations. Heme, a metabolite of erythrocyte degradation, was shown to be sufficient to induce *Spic* in bone marrow-derived macrophages. At steady state, red pulp macrophages continuously phagocytize senescent or damaged erythrocytes to recycle the iron from the heme-containing hemoglobin. Consequently, pathological depletion of red pulp macrophages leads to an accumulation of heme in the spleen. While *Spic* expression in monocytes is constitutively inhibited by BACH1, the presence of heme induces its proteasomal degradation, thereby allowing SPIC to be expressed by monocytes that will reconstitute the red pulp macrophage population [45]. Other genes repressed by BACH1 include ferroportin-1 (*Fpn1*), which is involved in iron export [46] and heme oxygenase-1 (*Hmox1*), essential for heme catabolism [47]. In addition to being essential for red pulp macrophage function, HMOX1 is critical for their survival, as accumulation of heme is cytotoxic [48]. Thus, in the *Spic*$^{-/-}$ deficient mouse model the inability of macrophages to express SPIC in the red pulp may hinder their capacity to perform splenic red pulp-specific functions, rendering them unable to survive in the red pulp. In essence, SPIC is important for both the functional maturation of red pulp macrophages and their survival. The discovery of heme as the driver of red pulp macrophage development was the first time a metabolic-driven differentiation of macrophages was described [45].

### 3.2. Marginal zone macrophages and metallophilic macrophages

Next to red pulp macrophages, the spleen also contains marginal zone macrophages and metallophilic macrophages [49]. Both are located in the marginal zone of the spleen, where they play a major role

Download English Version:

https://daneshyari.com/en/article/8943857

Download Persian Version:

https://daneshyari.com/article/8943857

Daneshyari.com