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Molecular and epigenetic basis of macrophage polarized activation

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ABSTRACT

Macrophages are unique cells for origin, heterogeneity and plasticity. At steady state most of macrophages are derived from fetal sources and maintained in adulthood through self-renewing. Despite sharing common progenitors, a remarkable heterogeneity characterized tissue–resident macrophages indicating that local signals educate them to express organ-specific functions. Macrophages are extremely plastic: chromatin landscape and transcriptional programs can be dynamically re-shaped in response to microenvironmental changes. Owing to their ductility, macrophages are crucial orchestrators of both initiation and resolution of immune responses and key supporters of tissue development and functions in homeostatic and pathological conditions. Herein, we describe current understanding of heterogeneity and plasticity of macrophages using the M1–M2 dichotomy as operationally useful simplification of polarized activation. We focused on the complex network of signaling cascades, metabolic pathways, transcription factors, and epigenetic changes that control macrophage activation. In particular, this network was addressed in sepsis, as a paradigm of a pathological condition determining dynamic macrophage reprogramming.

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1. Introduction: Macrophages are unique immune cells for origin, heterogeneity and plasticity

Macrophages are crucial orchestrators of both initiation and resolution of immune responses, and also key supporters of tissue development and functions under both homeostatic and pathological conditions [1–3]. Macrophages can coordinate this broad spectrum of diverse activities because they are endowed of an extraordinary plasticity and diversity [4]. Over the last five years, the development of genetic fate-mapping techniques has allowed to re-write macrophages ontogeny [5–10]. Hitherto, macrophages emerge as the only immune cell type that, in different proportion depending on the organ, are established during embryonic development and maintained in adulthood through longevity and local self-renewal [1,3,5–13]. These prenatal-derived macrophages represent the majority of steady state macrophages in tissues such as liver (Kupffer cells), brain (microglia), epidermis (Langerhans cells), lungs (alveolar macrophages) and heart [5–10,12,13]. In few tissues, like dermis and gut, tissue macrophages are constantly replenished by adult hematopoietic stem cells (HSC)-derived monocytes [14–16]. Macrophages with dual origin (embryonic and adult HSCs-derived) co-exist in organs such as spleen, kidney and pancreas [11]. Some controversial results are reported in tissue like peritoneum, where both embryonic [7,8] and adult bone marrow (BM)-derived [12] origin are suggested. Further, with the exception of microglia, widely recognized as yolk sac derived, the nature of

Abbreviations: HSCs, hematopoietic stem cells; EMPs, erythro-myeloid progenitors; LCs, Langerhans cells; BM, bone marrow; TRAP, Tartrate-resistant acid phosphatase; RP, red pulp; MZ, marginal zone; AMs, alveolar macrophages; IMs, interstitial macrophages; PIMs, pulmonary intravascular macrophages; LPS, Lipopolysaccharide; SOCS, suppressor of cytokine signaling; PGE2, prostaglandin E2; STAT, Signal Transducer and Activator of Transcription; DMs, dermal macrophages; LDTFs, lineage-determining transcription factors; GATA6, GATA-binding protein 6; GM-CSF, Granulocyte-macrophage colony-stimulating factor; PPARγ, peroxisome proliferator-activated receptor-γ; RANK, Receptor activator of nuclear factor kappa-B; LXRα, transcription factors liver X receptor α; iNOS, inducible nitric oxide synthase; NO, nitric oxide; ROS, reactive oxygen species; IRF, Interferon Regulatory Factor; PFK2, 6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase; CARKL, carbohydrate kinase-like protein; IDH, isocitrate dehydrogenase; FFAs, free fatty acids; FAO, fatty acid oxidation; PGC-1β, PPARγ-coactivator-1β; COX, cyclooxygenase; HIFs, Hypoxia Inducible Factors; KLFs, Kruppel-like transcription factors; TLRs, Toll like receptors; TAMs, tumor associated macrophages; PGK, Phosphoglycerate kinase; LAL, lysosomal acid lipase; PDK1, pyruvate dehydrogenate kinase 1; AMPK, adenosine monophosphate kinase; PTEN, tensin homolog deleted on chromosome 10; mTOR, Mechanistic Target of Rapamycin; HDAC, Histone deacetylases; MLL, Myeloid Lymphoid Leukaemia; SHIP-1, phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase 1; SIRT1, sirtuin 1.

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the prenatal precursors is still under debate. Recently, using three different inducible fate mapping mice (Csf1r^{MercreMer}, Tie2^{MercreMer} and Flt3-Cre) Gomez Perdiguero et al. identified erythro-myeloid progenitors (EMPs) in the yolk sac as the precursor of all embryonic-derived macrophages in the adult tissues [10]. In contrast using Kit (CD117) gene to create an inducible fate mapping mice, Sheng and colleagues indicate that brain microglia and, to some extent, epidermal LCs are the only yolk-sac derived macrophages because they are the unique cells that can be detected when EMPs are labeled before generation of pre-HSCs in the intra-embryonic mesoderm [12]. Labeling HSCs-dependent hematopoiesis, all adult non-microglial tissue-resident macrophages and peripheral blood cells are similarly detected, indicating an HSCs origin [12]. In agreement, combining *in vivo* yolk sac macrophages depletion with several fate-mapping models of yolk sac macrophages and/or fetal liver monocytes, Hoeffel et al. claim that only microglia derived from yolk sac ckit$^+$Csfr1$^+$ EMPs without passing through fetal monocytes [13]. However, Hoeffel and colleagues indicate that a second wave of progenitors give rise to late definitive EMPs which, following the establishment of blood circulation, migrate to the liver where they acquire c-Myb expression and give rise to fetal monocytes [13]. Hence, these late c-Myb$^+$ EMPs, instead of HSCs, are indicated as the principal source of fetal monocytes that then seeded embryonic tissues and differentiated into macrophages [13].

Pioneering studies suggest that human macrophages ontogeny resemble the murine one [17,18]. Indeed, the analysis of radio-resistant Langerhans cells (LCs) from patients that underwent HSCs transplantation, as well as of human hand allograft biopsy, have showed that epidermal macrophages are maintained up to 10 years suggesting a great longevity or a self renewal capacity [17,19,20]. Moreover, the presence of a normal number of LCs and tissue macrophages in patients carrying a syndrome characterized by a defective hematopoiesis associated with monocytopenia and absence of peripheral DCs, B and NK lymphoid cells, suggests that human macrophages origin and maintenance are largely bone marrow (BM)-independent [21].

Despite sharing common progenitors, tissue-resident macrophages show distinct transcriptional [22,23] and epigenetic signatures [23,24], suggesting that local microenvironmental signals educate them to express organ-specific functions. Indeed, when transplanted BM precursors are seeded to the different tissues, their chromatin landscape is reshaped according to local signals to whom they are exposed [23]. Even tissue macrophages can be reprogramed when transferred into a new microenvironment, indicating that epigenetic chromatin marks are dynamic and that, macrophages retain plasticity, even if they are terminally differentiated cells [23]. Further, in a mouse model where host (embryonic) coexist with donor (post-natal)-derived AMs, the transcriptional profiles of both population are largely similar, suggesting that microenvironment dictates gene expression with the exception of few genes that remain linked to cellular origin [25].

Beside physiological local signals, macrophages can finely shape their functional phenotype in response to the micro environmental cues that they sense [26–30]. The identification of “latent” or “de-novo” enhancers, which are distal regulatory elements that gain and retain histone modifications only upon stimulation [31,32], further supports the epigenetic plasticity of macrophages in response to external stimuli. Owing to their ductility, macrophages play a key role in both host defense and tissue homeostasis, however the ability of macrophages to reprogram their functions acts as a double edged sword in several pathological conditions [33–37]. Hence, dissecting the molecular basis of macrophages biology will enable new macrophage-centered strategies with promising therapeutic value for a wide range of human diseases [1,2,34]. Here, we will describe current understanding of heterogeneity and plasticity of macrophages, focusing on the complex network of signaling cascades, metabolic pathways, transcription factors, and epigenetic changes that controls macrophage activation.

2. Hallmarks and regulation of physiological macrophage heterogeneity

A remarkable heterogeneity characterizes tissue-resident macrophages. Indeed, not only multiple functional macrophage subtypes have been identified in different organs, but even within the same tissue, macrophages located in specific anatomical sites exhibit distinct trophic activities [4].

In the bone, Tartrate-resistant acid phosphatase (TRAP)$^+$ F4/80$^+$ osteoclasts participate in bone remodeling by reabsorbing bone tissue [38,39], whereas TRAP$^-$ CD169$^+$ F4/80$^+$BM macrophages are crucial component of the erythroid niche, supporting red blood cells development and uptake of the nuclei extruded by erythroid precursors [40,41].

In the spleen, three different subsets of macrophages can be distinguished: (1) F4/80$^+$ CD68$^+$ macrophages, localized in the red pulp (RP) and specialized in the clearance of senescent erythrocytes and iron recycling; (2) F4/80^{lo}CD68^{Hi} MFG-E8^{Hi} macrophages, situated in the white pulp (WP) and committed to the phagocytosis of apoptotic lymphocytes; (3) CD169$^+$SIGN-R1$^+$MARCO$^+$TIM-4$^+$ macrophages, located at the marginal zone (MZ) where they initiate immune responses against blood-borne particulate antigens [42,43].

Accumulating evidence indicate that three different macrophage populations coexist even in lungs: (1) alveolar macrophages (AMs) are located on the luminal side of alveolar epithelium behind surfactant; (2) interstitial macrophages (IMs) reside in the narrow space limited by alveolar epithelium and vascular endothelium; (3) pulmonary intravascular macrophages (PIMs) are blood monocytes-derived macrophages that adhere to endothelium of pulmonary capillaries [44,45]. AMs originate from pre-natal precursor and are characterized by a rounded morphology, intense autofluorescence and the expression of F4/80, CD11c, CD64, lectins (*e.g.* CD206 and SiglecF) and scavenger receptors (*e.g.* SR-AI/II and MARCO), but not CD11b and CD24 [3,46–50]. In contrast, during both acute and chronic lung inflammation two additional populations of CD11c^{high}CD11b$^+$phagocytesand CD11c$^-$CD11b^{high} monocytes appear in the alveolar interspace [46]. Resident AMs are mainly involved in the clearance of surfactant [51] and of inhaled antigens [52] minimizing lung injury [53]. AMs are committed to limit local inflammation through different mechanisms, including regulatory circuits based on macrophages-epithelial communication. Using real-time alveolar imaging *in situ*, Westphalen and collegues showed that a subset of AMs is connected with the epithelium by connexin 43-containing gap junction channels and due to these interconnections, AMs spread immunosuppressive Ca^{2+} waves to restrain lipopolysaccharide (LPS)-induced inflammation [54]. The transcellular delivery of vesicular suppressor of cytokine signaling (SOCS) proteins from AMs to alveolar epithelial cells represents another inhibitory strategy [55]. At steady state, alveolar epithelial cells contribute to the production of anti-inflammatory signals such as prostaglandin E2 (PGE2) and IL-10, which induce AMs to secrete exosomes and microparticles containing SOCS1 and SOCS3 proteins. In turn the uptake of vesicular SOCS proteins by alveolar epithelial cells inhibits cytokines signaling by blocking Signal Transducer and Activator of Transcription (STAT) activation. In contrast, in response to LPS or cigarette smoke, SOCS secretion into airway fluid is reduced; the elimination of this brake enhances inflammation and likely contributes to the pathogenesis of inflammatory lung diseases [55].

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