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Redox-signals and macrophage biology (for the upcoming issue of molecular aspects of medicine on signaling by reactive oxygen species)

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ABSTRACT

Macrophages are known for their versatile role in biology. They sense and clear structures that contain exogenous or endogenous pathogen-associated molecular patterns. This process is tightly linked to the production of a mixture of potentially harmful oxidants and cytokines. Their inherent destructive behavior is directed against foreign material or structures of 'altered self', which explains the role of macrophages during innate immune reactions and inflammation. However, there is also another side of macrophages when they turn into a tissue regenerative, pro-resolving, and healing phenotype. Phenotype changes of macrophages are termed macrophage polarization, representing a continuum between classical and alternative activation. Macrophages as the dominating producers of superoxide/hydrogen peroxide and nitric oxide are not only prone to oxidative modifications but also to more subtle signaling properties of redox-active molecules conveying redox regulation. We review basic concepts of the enzymatic nitric oxide and superoxide production within macrophages, refer to their unique chemical reactions and outline biological consequences not only for macrophage biology but also for their communication with cells in the microenvironment. These considerations link hypoxia to the NO system, addressing feedforward as well as feedback circuits. Moreover, we summarize the role of redox-signaling affecting epigenetics and reflect the central role of mitochondrial-derived oxygen species in inflammation. To better understand the diverse functions of macrophages during initiation as well as resolution of inflammation and to decode their versatile roles during innate and adaptive immunity with the entire spectrum of cell protective towards cell destructive activities we need to appreciate the signaling properties of redox-active species. Herein we discuss macrophage responses in terms of nitric oxide and superoxide formation with the modulating impact of hypoxia.

Introduction

Macrophages are a group of heterogeneous cells of the innate immune system. Their purpose is to maintain homeostasis throughout the organism in a tissue-specific manner. Macrophages respond to and aim to repair disturbances in tissue homeostasis, thereby shaping initiation, progression, and resolution of inflammation (Lavin and Merad, 2013; Wynn et al., 2013). Their impact ranges from determining tissue architecture in the embryo, where they are involved in the generation of bone, adipose tissue, branching morphogenesis and vascular patterning, to rearranging extracellular matrix, taking up and recycling cellular and molecular debris, initiating and terminating inflammatory and growth signaling cascades, inducing cell migration, and killing as well as devouring malignant cells in the adult (Pollard, 2009; Wynn et al., 2013). To fulfil these tasks, macrophages sense and respond to a great variety of stimuli and rapidly change their functional repertoire to meet the demands of the current microenvironment. The importance of macrophages in tissue homeostasis is revealed by

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Abbreviations

ARG1	arginase 1
ECSIT	evolutionary conserved signaling intermediate in toll pathways
HDAC	histone deacetylases
HIF	hypoxia inducible factor
IFN-γ	interferon-γ
IL	interleukin
IRF	interferon regulatory factor
KDM	lysine demethylases
LPS	lipopolysaccharide
MAPK	mitogen activated protein kinase
MAVS	mitochondrial anti-viral signaling protein
MHC	major histocompatibility complex
NF-κB	nuclear factor-κB
NLRP3	NACHT, LRR and PYD domains-containing protein 3
(i)NOS	(inducible) NO-synthase
NOX	NADPH-oxidase
PHD	prolyl hydroxylases
PKC	protein kinase C
PPAR	peroxisome proliferator-activated receptor
(mt)ROS	(mitochondrial-derived) reactive oxygen species
STAT	signal transducer and activator of transcription
TLR	toll-like receptor
TNFα	tumor necrosis factor-α
TRAF	tumor necrosis factor receptor-associated factor
UCP2	mitochondrial uncoupling protein 2

their apparent dysfunction in human disease. Pathologies such as autoimmune diseases, atherosclerosis, fibrotic diseases, and cancer are characterized by disturbed or overshooting macrophage responses (Murray and Wynn, 2011; Wynn et al., 2013). Therefore, exploring macrophage biology may reveal novel strategies to combat leading causes of premature death in humans. Redox reactions are a vital component of the physiological and pathophysiological repertoire of macrophages, with redox-active molecules being produced to affect other cells and molecules as well as shaping the macrophage function in inflammation itself. In the following paragraphs, we therefore highlight the current state of the literature on macrophage redox biology and its impact on disease.

Understanding the complexity of macrophage functions

Based on their major importance in human disease, understanding macrophage diversity has been a major focus of research in the last years. Three main factors during a macrophage's lifespan determine its function, probably with different magnitude. First, developmental origin, i.e. at which time during the organismal life-span or from which precursor macrophages are produced, second, the specific microenvironment of the tissue the macrophage precursor or the mature macrophage migrates to in order to become sessile, and third, subsequent disturbances in tissue homeostasis that create stimuli triggering various macrophage functional responses (Fig. 1).

These three programs likely affect macrophage function at the transcriptional level (Smale et al., 2014). Distinct macrophage precursors may be characterized by a different transcriptional, i.e. gene expression profile (van de Laar et al., 2016), and an associated chromatin structure. This may yield different mature macrophage identities, although all macrophages express the lineage-determining transcription factor PU.1 that defines the macrophage core chromatin landscape, i.e. regions of open chromatin (Jenkins and Hume, 2014). PU.1 expression is triggered by the growth factors colony stimulating factor-1 (CSF1) or interleukin-34 (IL)-34, both of which signal through colony stimulating factor-1 receptor to sustain macrophage identity (Heinz et al., 2010; Jenkins and Hume, 2014). On top of the PU.1-dependent chromatin landscape transcription factors induced by tissue-specific cues shape the tissue-specific macrophage phenotype that is required to sustain local homeostasis. In addition, diverse mediators disrupt homeostasis, which activates transcriptional enhancers or repressors to allow macrophages to respond to these stimuli with the appropriate functional output. Together, they create the multitude of diverse macrophage phenotypes that have been reported. The relative contribution of the three layers of signal qualities indicated above is still poorly defined, but data acquired during the last decade provide clues on this topic as discussed below.

The impact of ontogeny on macrophage diversity

The current view on tissue macrophage ontogeny has been recently reviewed in detail (Bain et al., 2016; Guilliams and Scott, 2017; Mass et al., 2016). Briefly, when considering the origin of tissue macrophage in the adult, the prevalent view from the 1970s was that bone marrow-derived monocytes are immediate and continuously required precursors of terminally differentiated, non-proliferating, short-lived tissue macrophages (van Furth et al., 1972). This view was immediately challenged by observations that early hematopoietic events during fetal or embryonic development can produce non-monocytic macrophage progenitors that differentiate into long-lived cells, which self-sustain by local proliferation (Naito et al., 1996). The discrepancy of these opposing theories has apparently been resolved by recent studies. It appears that the majority of tissues are repeatedly populated during organismal development by macrophages that develop along different routes. The earliest macrophages develop from yolk sac-derived erythro-myeloid progenitors via a non-monocytic pre-macrophage intermediate and spread throughout the embryo after the establishment of a functional vasculature (Bain et al., 2016; Brune et al., 2017; Ginhoux and Jung, 2014; Guilliams and Scott, 2017; Hoeffel et al., 2015; Mass et al., 2016; Perdiguero et al., 2015). Simultaneously, these yolk sac-derived erythro-myeloid progenitors migrate to the fetal liver, where they later give rise to a second wave of macrophages, dependent or independent of a monocytic intermediate stage (Hoeffel et al., 2015; Perdiguero et al., 2015). This second wave of macrophage appears to replace the first macrophages in most tissues with the exception of the brain, because the blood-brain barrier is formed before the arrival of macrophages or their progenitors from the fetal liver (Ginhoux et al., 2010; Kierdorf et al., 2013; Schulz et al., 2012). Embryonic macrophages of either origin have the capacity to self-maintain their numbers by local proliferation (Bain et al., 2016; Epelman et al., 2014; Ginhoux and Jung, 2014; Guilliams and Scott, 2017; Mass et al., 2016). However, in some tissues such as the intestines and the dermis, macrophages indeed are short-lived and require replacement throughout life. These tissue macrophage populations are replenished by the third wave of macrophage progenitors, which are strictly hematopoietic stem cell-derived monocytes from the bone marrow (Bain and Mowat, 2014; McGovern et al., 2014). Generally, adult monocyte-derived macrophages show poor

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