Acta Biomaterialia 43 (2016) 3–13

Contents lists available at ScienceDirect

Acta Biomaterialia

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

Review article

Macrophage reaction against biomaterials in the mouse model – Phenotypes, functions and markers

R. Klopfleisch

Institute of Veterinary Pathology, Freie Universität Berlin, Robert-von-Ostertag-Straße 15, Berlin 14163, Germany

ARTICLE INFO

Article history:
Received 2 February 2016
Received in revised form 8 June 2016
Accepted 5 July 2016
Available online 6 July 2016

Keywords:
Macrophages
Biomaterials
Foreign body reaction
Biocompatibility
In vivo

ABSTRACT

The foreign body reaction (FBR) is a response of the host tissue against more or less degradation-resistant foreign macromolecular material. The reaction is divided into five different phases which involve most aspects of the innate and the adaptive immune system: protein adsorption, acute and chronic inflammation, foreign body giant cell formation and fibrosis. It is long known, that macrophages play a central role in all of these phases except for protein adsorption. Initially it was believed that the macrophage driven FBR has a complete negative effect on biocompatibility. Recent progress in biomaterial and macrophage research however describe macrophages as more than pure antigen phagocytosing and presenting cells and thus pro-inflammatory cells involved in biomaterial encapsulation and failure. Quite contrary, both, pro-inflammatory M1 macrophages, the diverse regulatory M2 macrophage subtypes and even foreign body giant cells (FBGC) are after necessary for integration of non-degradable biomaterials and degradation and replacement of degradable biomaterials. This review gives a comprehensive overview on the taxonomy of the currently known macrophage subtypes. Their diverging functions, metabolism and markers are summarized and the relevance of this more diverse macrophage picture for the design of biomaterials is shortly discussed.

Statement of Significance

The view on role of macrophages in the foreign body reaction against biomaterials is rapidly changing. Despite the initial idea that macrophage are mainly involved in undesired degradation and biomaterial rejection it becomes now clear that they are nevertheless necessary for proper integration of non-degradable biomaterials and degradation of placeholder, degradable biomaterials. As a pathologist I experienced a lack on a good summary on the current taxonomy, functions and phenotypes of macrophages in my recent projects on the biocompatibility of biomaterials in the mouse model. The submitted review therefore intends to gives a comprehensive overview on the taxonomy of the currently known macrophage subtypes. Their diverging functions, metabolism and markers are summarized and the relevance of this more diverse macrophage picture for the design of biomaterials is shortly discussed.

Contents

E-mail address: robert.klopfleisch@fu-berlin.de

http://dx.doi.org/10.1016/j.actbio.2016.07.003
1742-7061/

1. Introduction

Macrophages play a central role in the foreign body reaction (FBR) against macromolecular biomaterials like polymers and hydrogels. Morphologically, macrophages in the FBR are classically subtyped into macrophages, epitheloid cells and foreign body giant cells (FBGC). Recent research however shows that macrophages are a highly diverse population in terms of function and molecular phenotype [1–12]. Especially the notion that macrophage may either behave pro- or anti-inflammatory has put them in the spotlight of research on the host response against implanted biomaterials . The goal of this "macrophage-centered approach" is the understanding how the balance between pro- and anti-inflammatory and regulatory macrophages in FBR can be influenced by the structure of the biomaterial or additional treatments to allow for a functional tissue remodeling instead of extended inflammation, fibrosis and scarring [4]. Initially, a simple M1-/M2-dichotomy of pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages has been developed to describe the different functions of macrophages during inflammation and healing [13]. There is however an increasing number of studies which show that this model may be an oversimplification of the in vivo situation [1–12]. At least in the complex in vivo environment of inflammatory sites, macrophage phenotypes seem to be more variable than initially thought with more than two clearly discernable or even a wide spectrum of blending phenotypes and functions [1–12]. The present review is intended to give a compact overview on the current knowledge on sources, phenotypes, mechanisms of polarization, markers and functions of macrophages with a specific focus on the impact of these findings on biomaterial research.

2. Tissue macrophages in health – residents and immigrants

Resident macrophages are present in almost all tissues of the body. Depending on the location, they may have special names like hepatic Kupffer cells, cutaneous Langerhans cells, peritoneal macrophages pulmonary alveolar macrophages or central nervous microglial cells. Although all of them have similar "functional" phenotypes which includes the surveillance for and response to pathogens, phagocytosis and tissue repair, they are nevertheless characterized by unique gene expression patterns and thus different macrophage molecular subclasses.

Initially it was thought that tissue-resident macrophages are continuously replenished by migrating monocytes from the blood stream [14]. However, recent research draws a more differentiated and tissue-dependent picture of the origin of tissue-resident macrophages [15]. According to the currently available data, Italiani et al. suggested that resident tissue macrophages in healthy tissues have to be separated in two populations: "true" tissue-resident macrophages and monocyte-derived tissue macrophages which can be defined by tracing studies but not routinely in vivo in the tissue due to their so far indiscernible phenotype [8].

"True" tissue resident macrophages seed the tissue early during embryonic development directly from the ectoderm of the yolk sac (or the fetal liver) without going through the typical monocytic progenitor developmental stages [16–18]. They are characterized by self-renewal capacity, which leads to the question if at least a subpopulation of them may have stem cell-like features [6,8]. Microglial cells of the CNS and Langerhans cells of the epidermis seem to be the only true tissue resident macrophages [6,19]. There is an ongoing debate if and to what extent true tissue resident macrophages are still present in the adult lung, heart, kidney, pancreas, liver and the red pulp of the spleen [6,12,19–23].

Monocyte-derived tissue macrophages develop by migration of circulating monocytes into the tissues postnatally (Figs. 1 and 2A). Monocytes, which make up 2–4% of the circulating leukocytes in mice, are recruited to most tissues to replenish the resident tissue macrophages in health or are recruited in larger numbers to inflammation sites [8]. Murine monocytes are mainly subtyped by their expression level of lymphocyte antigen 6 complex (Ly6C). Ly6$^+$, "inflammatory" monocytes are mainly released from bone marrow and spleen after inflammation is recognized [12]. Under these circumstances they migrate into the tissue and mature into pro-inflammatory M1 macrophages. Migration into the

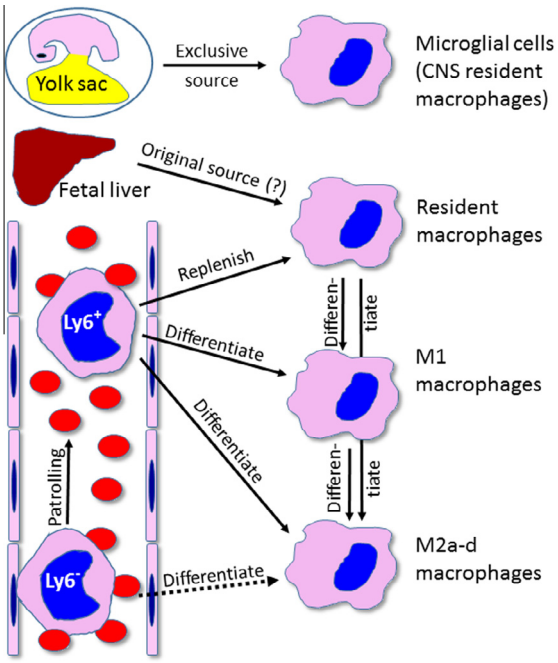

Fig. 1. The origin of tissue macrophages. Monocytes are replenishing resident tissue macrophages in health and are a source for inflammatory M1 and M2 macrophage in almost all tissues except in brain and in some extent in the epidermis. In these two tissues, resident macrophages (microglia and Langerhans cells) are thought to originate only from the ectoderm of the yolk sac or the fetal liver and to have self-renewal (stem cell-like) properties. During mild inflammation resident macrophages can most probably polarize to M1 or M2a-d macrophages. During a more severe inflammation, migrating Ly6$^+$ and maybe some Ly6$^-$ monocytes are believed to mature to M1 and M2a-d macrophages. However, the presented scheme is mainly based on data from in vitro experiments. The exact processes in the more multifactorial inflammation in vivo is in many aspects unclear.