Biochimica et Biophysica Acta 1865 (2016) 23–34

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Tissue-resident versus monocyte-derived macrophages in the tumor microenvironment

Qods Lahmar [a,b], Jiri Keirsse [a,b,1], Damya Laoui [a,b,1], Kiavash Movahedi [a,b,1], Eva Van Overmeire [a,b,1], Jo A. Van Ginderachter [a,b,*]

[a] Myeloid Cell Immunology Lab, VIB, Brussels, Belgium
[b] Lab of Cellular and Molecular Immunology, Vrije Universiteit Brussel, Brussels, Belgium

ARTICLE INFO

Article history:
Received 29 May 2015
Received in revised form 25 June 2015
Accepted 26 June 2015
Available online 2 July 2015

Keywords:
Tumor-associated macrophages
Tissue-resident macrophages
Monocyte-derived macrophages
Kupffer cell
Microglia
Breast cancer
Lung cancer
Pancreatic adenocarcinoma
Glioma
Hepatocellular carcinoma

ABSTRACT

The tumor-promoting role of macrophages has been firmly established in most cancer types. However, macrophage identity has been a matter of debate, since several levels of complexity result in considerable macrophage heterogeneity. Ontogenically, tissue-resident macrophages derive from yolk sac progenitors which either directly or via a fetal liver monocyte intermediate differentiate into distinct macrophage types during embryogenesis and are maintained throughout life, while a disruption of the steady state mobilizes monocytes and instructs the formation of monocyte-derived macrophages. Histologically, the macrophage phenotype is heavily influenced by the tissue microenvironment resulting in molecularly and functionally distinct macrophages in distinct organs. Finally, a change in the tissue microenvironment as a result of infectious or sterile inflammation instructs different modes of macrophage activation. These considerations are relevant in the context of tumors, which can be considered as sites of chronic sterile inflammation encompassing subregions with distinct environmental conditions (for example, hypoxic versus normoxic). Here, we discuss existing evidence on the role of macrophage subpopulations in steady state tissue and primary tumors of the breast, lung, pancreas, brain and liver.

1. Introduction

Macrophages are among the most plastic cells of the hematopoietic system. They are ubiquitous cells found in all tissues, in which they display functional and anatomical diversity. Macrophages are implicated in organogenesis and are key players in tissue homeostasis maintenance, tissue repair and immune surveillance.

The traditional belief that all tissue macrophages derive from hematopoietic stem cells (HSC) in the bone marrow via circulating monocyte precursors [1] has been overthrown in recent years. It has been shown that certain tissue-resident macrophage populations are already present in the embryo before the development of HSC (Fig. 1). Studies based on the inactivation of the transcription factor c-Myb, crucial for HSC development, confirmed that macrophages in adulthood can be derived from progenitor cells in the embryonal yolk sac [2]. These *Csf1r*$^+$ progenitors with erythro-myeloid potential (erythro-myeloid progenitors or EMP) emerge at embryonal day E8.5 in the mouse yolk sac [3] and either fully differentiate into tissue-resident macrophages without the presence of a monocyte intermediate (as is the case for microglia), or give rise to c-Myb$^+$ liver monocytes that seem to be the prime source of liver Kupffer cells (KC), epidermal Langerhans cells (LC), alveolar macrophages and possibly other tissue-resident macrophages [4]. Only following these events, a second wave of HSC-dependent hematopoiesis is initiated in the fetal liver [3]. Notably, full maturation of some tissue macrophages, such as alveolar macrophages, is only achieved early after birth [5]. Some of these tissue macrophages are very long lived and are hardly replaced by HSC-derived cells under steady-state (KC, microglia, LC) [2,6–9], while other macrophage populations are either rapidly replaced after birth (gut macrophages, [10]) or gradually replaced throughout life (alveolar macrophages [3]; heart macrophages [11–13]).

These studies raise the important question of determining the macrophage identity and function during a situation of chronic smoldering inflammation such as cancer. Tumor-associated macrophages (TAM) are the predominant leukocytes infiltrating solid tumors and can represent up to 50% of the tumor mass. The clinical significance of these cells is illustrated by the significant link between TAM number and density and a poor prognosis in 80% of the reported studies [14–16]. The non-redundant role of macrophages in tumor progression flows from the fact that TAMs actively contribute to each stage of cancer. They promote cancer cell invasion, metastasis and angiogenesis by

* Corresponding author at: Lab of Cellular and Molecular Immunology, VIB-Vrije Universiteit Brussel, Building E8, Pleinlaan 2, B-1050 Brussels, Belgium.
E-mail address: jvangind@vub.ac.be (J.A. Van Ginderachter).
[1] The authors contributed equally.

http://dx.doi.org/10.1016/j.bbcan.2015.06.009
0304-419X/

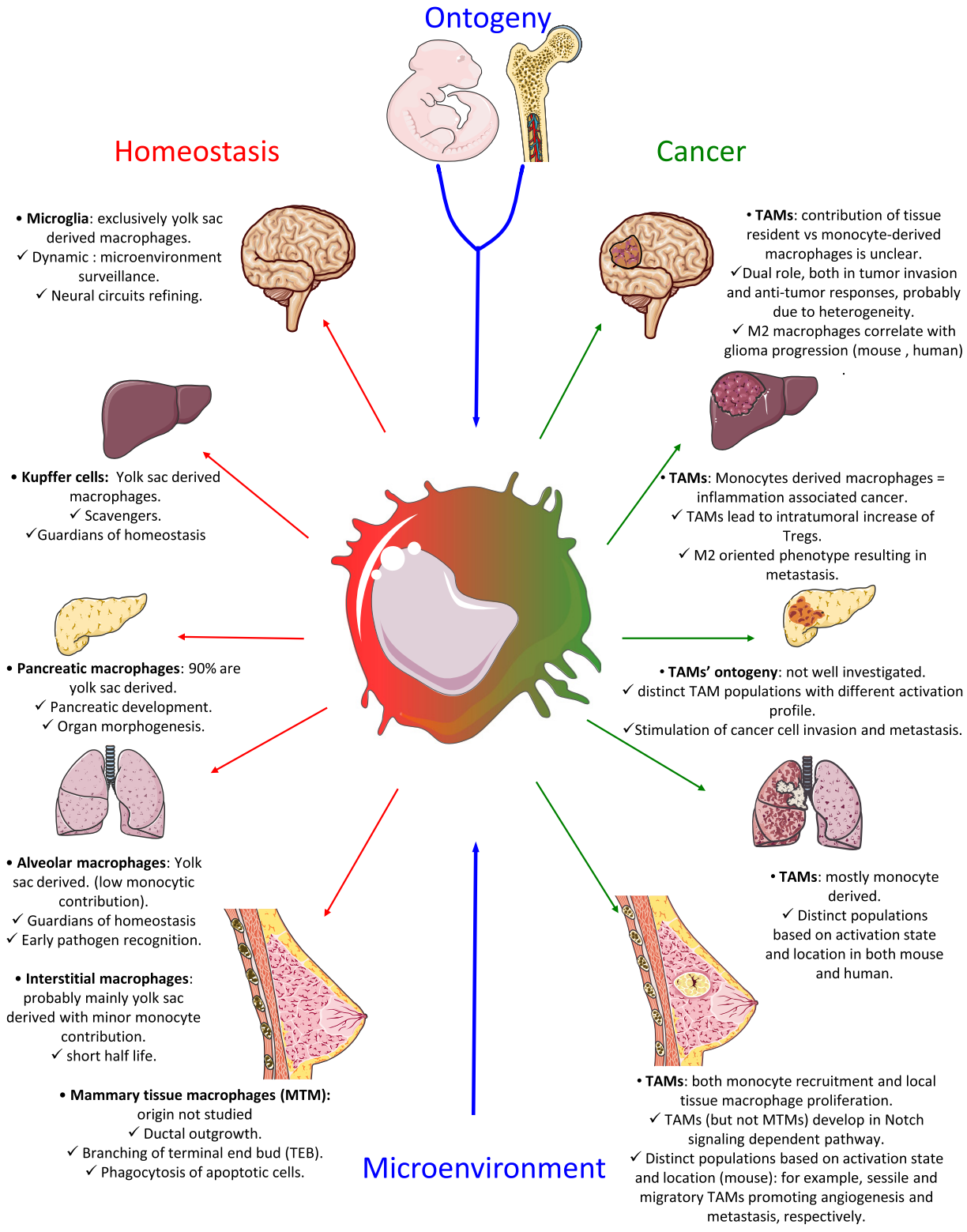

Fig. 1. Ontogenic, functional and anatomical diversity of macrophages under steady state or cancer conditions. Macrophage heterogeneity in a tissue can be the result of a different origin (yolk sac-derived/HSC-independent versus bone marrow-derived/HSC-dependent) but also the confrontation with a distinct microenvironment. Under homeostatic conditions (red), most tissue-resident macrophages are yolk sac-derived and perform specialized functions in each organ. During cancer (green), which is a type of chronic smoldering inflammation, the contribution of tissue-resident versus monocyte-derived macrophages to the tumor microenvironment is not always clear and might depend on the tumor type and afflicted tissue. Most often, tumor promoting functions have been ascribed to TAM and the involvement of M2-oriented macrophages (irrespective of their origin) seems to be a recurring theme in most organs.

releasing cytokines, growth factors, extracellular matrix-degrading enzymes and angiogenic factors including vascular endothelial growth factor (VEGF), Bv8 and MMP9. TAM also inhibit cytotoxic T-cell activity by the secretion of suppressive cytokines such as IL-10 and TGF-β, high levels of arginase activity and the production of ROS and RNI [17–21]. Finally, TAM can contribute to tumor relapse following tumor