EXPERIMENTAL CELL RESEARCH 319 (2013) 1626–1634

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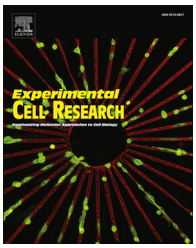

Review Article

Reciprocal interactions between endothelial cells and macrophages in angiogenic vascular niches

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ARTICLE INFORMATION

Article Chronology:
Received 22 December 2012
Received in revised form
20 March 2013
Accepted 21 March 2013
Available online 28 March 2013

Keywords:
Macrophage
Monocyte
Angiogenesis
Blood vessel
Heterotypic cell interaction
Microvesicle
Exosome

ABSTRACT

The ability of macrophages to promote vascular growth has been associated with the secretion and local delivery of classic proangiogenic factors (e.g., VEGF-A and proteases). More recently, a series of studies have also revealed that physical contact of macrophages with growing blood vessels coordinates vascular fusion of emerging sprouts. Interestingly, the interactions between macrophages and vascular endothelial cells (ECs) appear to be bidirectional, such that activated ECs also support the expansion and differentiation of proangiogenic macrophages from myeloid progenitors. Here, we discuss recent findings suggesting that dynamic angiogenic vascular niches might also exist *in vivo*, e.g. in tumors, where sprouting blood vessels and immature myeloid cells like monocytes engage in heterotypic interactions that are required for angiogenesis. Finally, we provide an account of emerging mechanisms of cell-to-cell communication that rely on secreted microvesicles, such as exosomes, which can offer a vehicle for the rapid exchange of molecules and genetic information between macrophages and ECs engaged in angiogenesis.

Contents

Abbreviations: ANG, Angiopoietin; CSF1, Colony stimulating factor-1; EC, Endothelial cells; ECM, Extracellular matrix; FGF2, Basic fibroblast growth factor; HPC, Hematopoietic progenitor cell; IL, Interleukin; MV, Microvesicles; NRP1, Neuropilin-1; PlGF, Placental growth factor; TAM, Tumor-associated macrophage; TEM, TIE2-expressing macrophage; TNFα, Tumor-necrosis factor-α; VEGF, Vascular-endothelial growth factor

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http://dx.doi.org/10.1016/j.yexcr.2013.03.026

Introduction

Macrophages are an important component of the innate arm of the immune system, as they constitute a first line of defense against invading pathogens. They engulf microbes and can present antigens to T-cells to promote specific (adaptive) immune responses. In addition, macrophages perform a broad array of functions beyond immune surveillance, and regulate tissue and organ growth, remodeling, and homeostasis. This is primarily achieved via their secretion of cytokines, growth factors, proteolytic enzymes, and expression of scavenger receptors that recognize multiple components of the extra-cellular matrix (ECM) [1,2]. Thus, macrophages play crucial roles in tissue morphogenesis (e.g., vascular and neuronal patterning) and patho-physiological conditions like inflammation and organ healing [3,4].

It has long been recognized that macrophages can support angiogenesis [5], the formation or expansion of new blood vessels during development and post-natal life [6,7]. Early reports showed that activated macrophages inoculated in the cornea of guinea pigs induced robust vascular proliferation [8], hence suggesting that these cells are an important source of proangiogenic signals. More recent studies have indeed revealed that (activated) macrophages are a source of multiple growth factors that can enhance endothelial cell (EC) proliferation and/or survival [9]. Furthermore, macrophages promote the remodeling of the ECM and provide survival and/or "guidance" cues to the ECs, both of which are important for EC migration and the (directional) growth of new blood vessels [10,11]. Finally, macrophages engage in tight cell-to-cell contacts with sprouting blood vessels to facilitate the "bridging" of endothelial sprouts during vascular anastomosis [12].

The proangiogenic functions of macrophages have been actively studied in the context of retinal and tumor angiogenesis. For example, abundant macrophages are observed in tumors, often in direct contact with the ECs of uncoated or partially coated tumor blood vessels [9,13–16]. These findings are consistent with the evaluation of human cancer specimens, in which high numbers of macrophages often correlate with increased angiogenesis [17,18]. Together, these data suggest that macrophages may exert direct proangiogenic functions in tumors. Indeed, mechanistic studies showed that depletion of monocytes/macrophages in tumor-bearing mice inhibits tumor angiogenesis and may delay cancer growth and progression [13,15;19–22].

In this review, we collate recent findings on the role of macrophages as regulators of angiogenesis. We further discuss the novel concept that EC-macrophage interactions are reciprocal: while macrophages regulate angiogenesis, ECs in turn provide signals that promote the expansion of proangiogenic macrophages within the perivascular microenvironment.

Proangiogenic functions of macrophages: role of secreted factors

Activated macrophages, such as tumor-associated macrophages (TAMs), secrete growth factors and inflammatory cytokines that can enhance EC activation, proliferation and survival (Fig. 1A). These include key proangiogenic mediators, such as vascular-endothelial growth factor (VEGF)-A, which activates the VEGF receptor (VEGFR)-2. Macrophages also express other VEGF family members, including placental growth factor (PlGF), which activates VEGFR-1; and VEGF-C, which activates VEGFR-3 and downstream NOTCH signaling [9,23]. Additional angiogenesis regulators expressed by macrophages include CXCL8, interleukin (IL)-1β, tumor-necrosis factor-α (TNFα), and basic fibroblast growth factor (FGF2). The functions of these cytokines, and the angiogenic responses triggered upon their binding to cognate receptors expressed on ECs, have been extensively reviewed elsewhere [9,24].

Macrophages activated during angiogenesis also secrete membrane-bound or soluble proteases that, via proteolytic digestion of the ECM, can mobilize proangiogenic growth factors embedded in the perivascular matrix. These include enzymes such as matrix-metalloproteinases (MMP-2, MMP-7, MMP-9, MMP-12) and serine/cysteine proteinases (urokinase, cathepsins, plasminogen activator) [24,25]. Furthermore, macrophages are thought to express "vascular guidance" molecules, like semaphorins, which modulate EC migration and survival [11,26]. Together with the matrix-remodeling activity of the many secreted proteases, the activity of macrophage-derived "vascular guidance" molecules may facilitate blood vessel sprouting and directional vascular growth through the ECM in tissues undergoing angiogenesis.

Recent findings also suggest that macrophages secrete microvesicles (MVs) that can deliver their cargo of macromolecules upon fusion with "acceptor" cells [27,28], possibly including ECs (Fig. 1A). Macrophage-derived MVs may thus have the potential to influence EC behavior via direct transfer of functional RNAs or proteins (see below).

Vascular-modulatory functions of macrophages: role of cell-to-cell contacts

Recent studies have suggested that, during fetal development, macrophages regulate vascular morphogenesis in the central nervous system by establishing cell-to-cell contacts with ECs (Fig. 1B, C).

Hindbrain angiogenesis

In the developing hindbrain, vascular growth follows two main steps, the first being the sprouting of pre-existing blood vessels and the second the fusion of such vascular sprouts with adjacent capillaries (a process known as vascular anastomosis). Whereas it