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Mast cells and basophils in inflammatory and tumor angiogenesis and lymphangiogenesis

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ABSTRACT

Angiogenesis, namely, the growth of new blood vessels from pre-existing ones, is an essential process of embryonic development and post-natal growth. In adult life, it may occur in physiological conditions (menstrual cycle and wound healing), during inflammatory disorders (autoimmune diseases and allergic disorders) and in tumor growth. The angiogenic process requires a tightly regulated interaction among different cell types (e.g. endothelial cells and pericytes), the extracellular matrix, several specific growth factors (e.g. VEGFs, Angiopoietins), cytokines and chemokines. Lymphangiogenesis, namely, the growth of new lymphatic vessels, is an important process in tumor development, in the formation of metastasis and in several inflammatory and metabolic disorders. In addition to tumors, several effector cells of inflammation (mast cells, macrophages, basophils, eosinophils, neutrophils, etc.) are important sources of a wide spectrum of angiogenic and lymphangiogenic factors. Human mast cells produce a large array of angiogenic and lymphangiogenic molecules. Primary human mast cells and two mast cell lines constitutively express several isoforms of angiogenic (VEGF-A and VEGF-B) and the two lymphangiogenic factors (VEGF-C and VEGF-D). In addition, human mast cells express the VEGF receptor 1 (VEGFR-1) and 2 (VEGFR-2), the co-receptors neuropilin-1 (NRP1) and -2 (NRP2) and the Tie1 and Tie2 receptors. Immunologically activated human basophils selectively produce VEGF-A and -B, but not VEGF-C and -D. They also release Angiopoietin1 that activates Tie2 on human mast cells. Collectively, these findings indicate that human mast cells and basophils might participate in the complex network involving inflammatory and tumor angiogenesis and lymphangiogenesis.

1. Introduction

The growth of blood vessels has fascinated scientists for centuries. Galen suggested that blood is locally regenerated by the body when its supply is consumed. Leonardo da Vinci proposed that blood vessels develop from the heart like a tree from the seed. William Harvey discovered that the heart pumps the blood through the arteries and the veins return the blood to the heart. In 1661 Marcello Malpighi discovered the capillaries and at the same time Caspar Aselius identified the lymphatic vessels. John Hunter coined the term “angiogenesis” in 1787 to describe the growth of new vessels (Carmeliet, 2005).

Angiogenesis, now defined as the growth of new blood vessels from pre-existing vasculature, is an essential process during embryonic and postnatal development (Marone and Granata, 2014). In adults, it occurs physiologically during the menstrual cycle and wound repair, as well as during inflammatory and autoimmune diseases and tumor growth (Ferrara, 2007; Marone et al. 2012). The lymphatic system develops in parallel, but secondarily to the blood vascular system through a process known as “lymphangiogenesis” (Alitalo, 2011; Simons and Eichmann, 2013). Angiogenesis and lymphangiogenesis are reactivated during wound healing and repair, in tumor growth and in chronic inflammation (Kim et al., 2012). In these conditions, the balance between stimulatory and inhibitory factors results in a (lymph)angiogenic switch (Varricchi et al., 2015).

2. Angiogenic and anti-angiogenic factors

In 1983 Harold Dvorak and collaborators isolated a factor that they called “Vascular Permeability Factor” (VPF) in cell-free

Abbreviations: AD, atopic dermatitis; Ang, angiopoietin; CAM, chorioallantoic membrane; CBMC, cord blood-derived mast cells; CFR_1, corticotrophin-releasing hormone receptor; CRH, corticotrophin-releasing hormone; EC, endothelial cell; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; HLMC, human lung mast cell; HSMC, human skin mast cell; PlGF, placental growth factor; sVEGFR-1, soluble VEGFR-1; VEGF, vascular endothelial growth factor; VPF, vascular permeability factor.

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supernatants from a variety of human and animal tumor cells (Senger et al., 1983). VPF was found to be an extremely potent permeability factor several logs more potent than histamine. Subsequently, Napoleone Ferrara and collaborators reported the purification and sequencing of an endothelial cell-specific mitogen which they called "Vascular Endothelial Growth Factor" (VEGF) (Leung et al., 1989). The molecular cloning of VEGF proved it to be the same VPF discovered earlier by Harold Dvorak (Keck et al., 1989). VEGF is the most specific growth factor for vascular endothelium (Ferrara, 2007). VEGF is not a single protein but a small menagerie of several peptides (Gerber et al., 2002). VEGF-A and -B are key regulators of blood vessels. Recent studies from Ulf Eriksson's laboratory have demonstrated that VEGF-B is a critical regulator of energy metabolism of endothelial cells (ECs) (Hagberg et al., 2010; 2012).

Several components of the VEGF family have different spliced forms that vary in their angiogenic effects. For instance, human VEGF-A has at least 6 isoforms: 121, 145, 165, 183, 189, and 204. VEGF-A_{165} is the most potent pro-angiogenic isoforms (Keyt et al., 1996). Conventional splice variants, including the most common isoforms, have been shown to be pro-angiogenic, exerting their effects by activating the VEGF receptor 2 (VEGFR-2) and VEGF receptor 1 (VEGFR-1) expressed by endothelial cells (ECs).

Placental growth factor (PlGF) was the second member of VEGF family to be discovered, having been cloned from human placental cDNA library (Maglione et al., 1991). Again, isoforms exist as a result of alternative splicing (Maglione et al., 1993).

Harper and Bates demonstrated that two families of VEGF-A isoforms can be found in humans, the pro-angiogenic isoforms typified by VEGF-A_{165}a and anti-angiogenic isoforms typified by VEGF-A_{165}b (Bates et al., 2013). VEGF-A_{165}b is expressed in normal cells and tissues and is circulating in human plasma (Woolard et al., 2004). These isoforms arise from differential splicing of exon 8: proximal splice site usage results in an mRNA containing the initial 19 nucleotides of exon 8a, coding for the proangiogenic VEGF-A_{165}a, whereas distal splice site usage results in expression of exon 8b and the antiangiogenic VEGF-A_{165}b that binds VEGFR-2 with the same affinity as VEGF-A_{165}, but does not activate or stimulate downstream signaling pathways. Moreover, it prevents VEGF-A_{165}a-mediated VEGFR-2 phosphorylation and signaling in cells. Therefore, VEGF-A_{165}b is not angiogenic and it inhibits VEGF-A_{165}a-mediated angiogenesis in vitro and in vivo. Interestingly, Matucci-Cerinic and collaborators have demonstrated that over-expression of VEGF-A_{165}b leads to insufficient angiogenesis in patients with systemic sclerosis (Manetti et al., 2011). More recently, VEGF-A_{165}b has been positively associated with inflammatory myopathies (Volpi et al., 2013) and peripheral artery disease (Kikuchi et al., 2014) and negatively associated with cancer (Peiris-Pages, 2012).

Thrombospondin is an endogenous inhibitors of angiogenesis, which prevents VEGF-induced angiogenesis by directly binding to it (Gupta et al., 1999). Endostatin also antagonizes the effects of VEGF (Yamaguchi et al., 1999).

Kari Alitalo and his collaborators have intensively investigated many fundamental pathophysiological aspects of lymphangiogenesis (Alitalo, 2011). In particular, they have isolated and cloned VEGF-C and VEGF-D and their receptor VEGFR-3 showing that this receptor is essential for lymphangiogenesis (Leppanen et al., 2011, 2013).

VEGFs signal through three human members of the VEGFR family expressed on blood ECs (BECs) and lymphatic ECs (LECs): VEGFR-1 and VEGFR-2 are present on BECs, whereas LECs express mainly VEGFR-3. The production of an alternative mRNA variant of VEGFR-1, soluble VEGFR-1 (sVEGFR-1) modulates the functions of VEGFs. In addition to the VEGFRs, two transmembrane glycoproteins, neuropilin-1 (NRP1) and neuropilin-2 (NRP2), have been identified as co-receptors for VEGFs (Zachary, 2014; Soker et al., 1998). NRP1 is expressed by BECs (Moyon et al., 2001) whereas NRP2 is expressed by venous and LECs (Zachary, 2014). NRP1 interacts with VEGF-A_{165}, but not VEGF-A_{121}, increasing the affinity of VEGF-A_{165} for VEGFR-2 and its phosphorylation, enhancing downstream signaling (Becker et al., 2005; Zachary, 2014).

Angiopoietins (Angs) are a family of growth factors essential for EC survival and maturation (Thomas and Augustin, 2009). In humans, Ang1 and Ang2 are the best characterized angiopoietins. The angiopoietin receptor system consists of two tyrosine kinase receptors (Tie1 and Tie2). Tie2 binds Ang1 and Ang2, whereas Tie1 is still considered an orphan receptor. Ang1 is primarily produced by mural cells and is a Tie2 agonist on ECs being essential for maturation of blood vessels. Ang2, almost exclusively produced by ECs, can function as a partial Tie2 agonist under certain experimental conditions (Yuan et al., 2009). The angiopoietin/Tie system plays a complex role in vascular development and is crucial for the angiogenic switch in tumors (Huang et al., 2010). Together with VEGFs, angiopoietins are the most important growth factors for proliferation, migration, and survival of vascular ECs. Moreover, Ang1 contributes to lymphatic vessel formation through the activation of Tie2 (Thomas and Augustin, 2009). Increasing evidence suggests that Angs are involved in human inflammatory diseases including asthma (Kanazawa et al., 2008; Prevete et al., 2013), and systemic lupus erythematosus (SLE) (Kumpers et al., 2009) in addition to cancer (Huang et al., 2010).

Angiogenin, produced by macrophages, ECs, and lymphocytes is one of the most potent tumor-derived angiogenic factors (Fett et al., 1985). Basic fibroblast growth factor (FGF-β) belongs to a group of heparin-binding growth factors that stimulate EC proliferation and play a role in wound healing and in angiogenesis (Broadley et al., 1989). In order to form new vessels during angiogenesis, ECs need to migrate, invade extracellular matrix (ECM), proliferate, and to re-establish new contacts with cells and the surrounding matrix. The urokinase (uPA)-mediated plasminogen activation (PA) system is a complex system of serine proteases involved in different phases of the angiogenic process (Montuori and Ragno, 2014). uPA is a potent chemoattractant for human basophils through the engagement of the surface receptor uPAR(de Paulis et al., 2004a).

Several cytokines (e.g. IL-17 and IL-25) (Corrigan et al., 2011; Starnes et al., 2001; Suryawanshi et al., 2012) and chemokines (e.g. CXCL8/IL-8) produced by immune cells are potent modulators of angiogenesis (Bosisio et al., 2014).

3. Mast cells and basophils as a source and target of angiogenic factors

In 1971 Judah Folkman, the father of angiogenic research, published a landmark review suggesting that tumor growth is angiogenesis-dependent and the inhibition of angiogenesis could be of therapeutic value (Folkman, 1971). Folkman also hypothesized that immune cells could be a source of angiogenic factors. In particular, he suggested that macrophages and mast cells could be a source of factors modulating tumor growth. He suggested that tumors would be unable to grow beyond a microscopic size of 1-2 mm^3 without continuous formation of new blood vessels. This observation, now widely accepted, was the basis of the concept of "anti-angiogenesis" as a potential novel anti-cancer therapy.

Tissue mast cells and circulating basophils are the only cells expressing the tetrameric high-affinity receptor (FcεRI) for IgE and synthesizing a myriad of proinflammatory and immunoregulatory molecules (Borriello et al., 2014a; Marone et al., 2014). These cells share some similarities, but play distinct roles in several aspects of innate and adaptive immunity (Borriello et al., 2014b; Marone et al., 2014).