EXPERIMENTAL CELL RESEARCH 319 (2013) 1271–1280

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

Review Article

Angiopoietin signaling in the vasculature

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ARTICLE INFORMATION

Article Chronology:
Received 3 November 2012
Received in revised form
3 March 2013
Accepted 4 March 2013
Available online 13 March 2013

Keywords:
Angiopoietin-1
Angiopoietin-2
Angpt
Tie1
Tie2
Tek
Receptor tyrosine kinase
Endothelial permeability
Vascular remodeling
Inflammation
Angiogenesis
Tumor angiogenesis
Lymphangiogenesis

ABSTRACT

The angiopoietin (Ang) growth factors and the endothelial Tie receptors regulate blood and lymphatic vessel development, and vascular permeability, inflammation, angiogenic remodeling and tumor vascularization in adult tissues. The angiopoietins activate the Tie receptors in unique *in trans* complexes at endothelial cell–cell and cell–matrix contacts. In addition, integrins have been implicated in the regulation of Ang–Tie signaling. Recent interest has focused on the function of angiopoietin-2 and its inhibition in the tumor vasculature and also in other pathological conditions associated with endothelial dysfunction. Here we review the current understanding of the signaling functions of the Ang–Tie pathway and its potential for future development of targeted vascular therapeutics.

Contents

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http://dx.doi.org/10.1016/j.yexcr.2013.03.011

Introduction

The angiopoietins and the Tie receptor tyrosine kinases, together with the vascular endothelial growth factors (VEGFs) and their receptors, form the two signaling pathways that are almost exclusively endothelial cell (EC) specific. The angiopoietins (Ang1, Ang2, Ang4, also termed Angpt) bind to Tie2 (also termed TEK). Most studies have focused on the functions of Ang1 and Ang2, and not much is known about Ang4 or its mouse orthologue, also termed Ang3. The Tie2 homolog Tie1 does not directly bind to the angiopoietins, and therefore its function in angiopoietin signaling is incompletely understood [1]. However, Ang1 activates Tie1, most likely via interaction with Tie2 [2,3], suggesting that Tie1 is part of the Ang–Tie signaling system.

Perivascular cells that coat mature vessels express Ang1 [4], while Ang2 is expressed by EC. Ang2 expression is increased in hypoxic and tumor blood vessels and is particularly high in the specialized tip cells of sprouting blood vessels [5,6]. Ang2 is stored in EC secretory granules called Weibel–Palade bodies and released locally in response to inflammatory stimuli [7]. Ang2 induces a weaker Tie2 tyrosyl phosphorylation than Ang1 [8]. Therefore, in situations where Ang2 levels are elevated, Ang2 may attenuate the more robust Ang1-induced Tie2 activation. In the lymphatic vessels and in tumor blood vessels, Ang2 itself may act as a Tie2 agonist [9,10].

The Tie receptors are expressed in the blood and lymphatic endothelium, and in certain hematopoietic cells, such as the Tie2 positive macrophages (TEMs) [11]. Tie1 expression is regulated by blood flow and shear stress [12,13], and increases during wound healing and in angiogenic tumor blood vessels [14], suggesting a function during tissue neovascularization.

Angiopoietins assemble to unique multimeric structures, and a tetrameric, or higher order multimer, is required for Tie2 activation [15]. This suggests that the active Tie receptor complex is composed of several receptor units, unlike classical receptor tyrosine kinases, which are activated by dimeric growth factors. The activation of Tie2 occurs via a unique, context-dependent mechanism, which is not used by other soluble growth factors (Fig. 1) [16,17]. In the presence of Ang1, the Tie receptors are rapidly translocated to cell–cell junctions, where they form homomeric complexes that associate *in trans* across the EC junctions [16,17]. At this subcellular location, the Ang1–Tie2 complexes mediate endothelial survival, stabilization and anti-inflammatory functions [16–19]. In mobile ECs, matrix-bound Ang1 activates Tie2 in cell–matrix contacts, where the Ang1–Tie2 complexes transduce signals for matrix adhesion and cell migration [16,17].

Ang–Tie system in lymphatic and blood vascular development

The Ang–Tie system is not required for the differentiation of ECs from progenitor cells (vasculogenesis), or for the initial formation of the lymphatic vasculature in embryos. However, components of the Ang–Tie pathway are required for the subsequent remodeling and maturation of the blood and lymphatic vasculatures during later phases of embryonic and postnatal development.

Tie2 deletion in mouse embryos results in severely impaired cardiac development, reduced numbers of ECs, hemorrhages, and death by embryonic day (E) 10.5 [20]. Analysis of embryos chimeric for the gene-targeted Tie2 allele showed that Tie2 is critical in the endocardium of the developing heart [21]. The gene-targeted embryos deficient of Ang1 have a very similar phenotype to that of Tie2 null embryos, and die by E12.5 [4]. The conditional deletion of Ang1 specifically in the cardiomyocytes phenocopies the constitutive Ang1 deletion, suggesting that the cardiac problems contribute to early vascular remodeling defects due to abnormal blood flow and hemodynamics [22].

The orphan Tie1 receptor is required for lymphangiogenesis, but is dispensable for lymphatic endothelial cell commitment during embryonic development [23,24]. The Tie1 deleted embryos, and embryos homozygous for a hypomorphic Tie1 allele were swollen, and their jugular lymph sacs were malformed [23,24]. The lymphatic defects were detectable at E12.5, before obvious changes in the blood vasculature, indicating that the lymphatic phenotype is not secondary to blood vascular defects [23,24]. The blood vasculature, however, is also affected in the Tie1 deleted embryos. Tie1 appears to be especially important for angiogenic capillary growth during later phases of blood vascular development, and Tie1 deletion results in compromised blood vascular integrity, hemorrhages and death of the embryos by E13.5-14.5 [25,26].

Embryos chimeric for the gene targeted alleles of both Tie1 and Tie2 showed a requirement for these receptors during the maturation and maintenance or survival of blood vascular ECs, as Tie1 and Tie2 deleted ECs were largely excluded from the developing blood vessels by E15.5 [21]. Intriguingly, Ang1 was dispensable for blood vascular development after E13.5, and is not needed for the homeostasis of the blood vasculature under normal conditions in adult mice [22]. This suggests that the Tie receptors may have Ang1 independent functions.

The ectopic overexpression of Ang2 in developing mouse embryos phenocopied the defects of Ang1 and Tie2 null embryos, suggesting that Ang2 acts as an antagonist of Ang1–Tie2 signaling during development [8]. However, mice deficient for Ang2 revealed that Ang2 was dispensable for blood and lymphatic vascular development during embryogenesis, but was required for postnatal remodeling of the vessels in specific vascular beds [9]. The major defects of the Ang2 null mice were in the lymphatic vasculature, resulting in profound and generalized lymphatic dysfunction, and the accumulation of chylous ascites [9]. These mice die within 2 weeks after birth, although some survive until adulthood, depending on the genetic background [9]. A closer analysis of Ang2 deleted mice revealed abnormal lymphatic vessel patterning and ectopic association of the lymphatic vessels with smooth muscle cells [9,27]. The blood vascular defects of Ang2 deficient mice are mainly limited to the developing