Editorial

Enhancement of new vessel formation by Angiopoietin-2/Tie2 signaling in endothelial progenitor cells: A new hope for future therapy?

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The Tie2/angiopoietin pathway is crucial for angiogenesis, blood vessel maturation, and vascular endothelial integrity. The ligands for Tie2 are the angiopoietins, of which angiopoietin-1 (Ang1) and Ang2 have been the most studied. Suppression of plasma leakage, inhibition of vascular inflammation, and prevention of endothelial death are the three widely accepted vascular protective functions for Ang1 [1], the first ligand identified for the Tie2 receptor. However, the role of Ang2, a relative of Ang1 identified by homology screening, remains less clear, because Ang2 exhibits context-dependent behavior. Ang2 can inhibit or stimulate Tie2 receptor phosphorylation under different experimental conditions [2]. Ang2 in vivo acts as a Tie2 antagonist on vascular endothelial cells (ECs), whereas it acts as a Tie2 agonist on lymphatic vessels [3]. Recently, increased Ang2 expression was demonstrated in myocardial ischemia and infarction [4,5], indicating the role of Ang2 in the angiogenic response to tissue ischemia.

In this issue of Cardiovascular Research, Kim et al. [6] report a proangiogenic activity of Ang2 in endothelial progenitor cells (EPCs) directly through the Tie2 signaling pathway. Ang2 increased tube formation, migration, and cell survival of EPCs derived from human umbilical cord blood CD34+ cells. Ang2 also increased EPC-mediated new vessel formation in vivo. This could not be demonstrated for mature endothelial cells (HUVECs) where Tie2 receptors were found to form heterocomplexes with Tie1. The authors clearly show that the differential reactivity of Ang2 in HUVECs is mediated by a physical association between Tie1 and Tie2 that inhibits Ang2-mediated Tie2 activation. Kim et al. [6] have used immunoprecipitation, Western blot analysis, and the siRNA technique to prove that the formation of the Tie1/Tie2 heterocomplex has a specific role in the ability of the Tie1 receptor to modulate the angiogenic properties of EPCs as compared to mature ECs. This work should open new opportunities for investigation, such as exploration of the mechanism by which the Tie1 receptor inhibits Tie2 activation when forming a heterocomplex. Does the heterocomplex bind to Ang2? Does the interaction of Ang2 with the heterocomplex trigger a rapid internalization process that prevents Ang2 from activating downstream signaling pathways? Does the heterocomplex of Tie1/Tie2 induce rapid degradation or conformational change of Tie2 to inhibit the binding of Ang2?

Ang2 has been demonstrated to enhance expansion of endothelial cell progeny from human cord blood CD34+ progenitors, and cord blood cells can secrete Ang1 and Ang2 [7]. Ang2 causes a marked stimulation of EPC migration and adhesion, but does not have the same effect on ECs [8]. These findings imply that Ang2 plays a role as a regulator of endothelial development from circulating progenitors and suggest that Ang2 has a function in postnatal angiogenesis. The finding that Ang2 enhances EPC proangiogenic activity is important for further clinical therapeutics because strategies involving administration of a single angiogenic agent may not result in optimal angiogenesis. Cell therapies for the regeneration of myocardial tissue are among the hottest topics in cardiology today [9]. Risk factors for coronary artery disease correlate with a reduced number and functional activity of circulating endothelial progenitor cells.
Umbilical cord blood appears to be a robust source for isolating endothelial progenitor cells and hematopoietic stem cells, and the EPCs derived from cord blood have a greater proliferative activity than those derived from adult peripheral blood [11]. Stem cells combined with gene transfer could be synergistically more powerful than either alone for therapeutic angiogenesis and vasculogenesis [12]. Kim et al. [6] report on the proangiogenic activity of Ang2 on EPCs derived from human umbilical cord blood CD34+ cells. However, there are many kinds of stem cells [9], and different stem cells may have different characteristics and possibly different therapeutic effects on angiogenesis or vasculogenesis. It is not known whether Ang2 has the same proangiogenic effect on other stem cell types.

Although Ang2 was not shown to have a proangiogenic effect on HUVECs by Kim et al. [6], Harfouche and Hussain recently reported that Ang2 increased Tie2 phosphorylation and promoted cell survival on HUVECs [13]. The discrepancy between the two studies needs further clarification. Recent studies have shown that Ang2 treatment under particular conditions could stimulate Tie2 autophosphorylation and promote endothelial cell survival [2,14]. Ang2 is presumed to destabilize blood vessels by interfering with the Ang1-Tie2 signals and with endothelial–periendothelial cell interactions [15]. Increased expression of Tie2 and VEGF was observed in hypoxic or ischemic areas [4]. Potential interaction between the Ang2, Tie2, and VEGF pathways has to be considered. Therefore, the expression of Ang2 and VEGF during the same period of tissue ischemia may provide a drive for sprouting angiogenesis.

Recently, Ang2 has been demonstrated to induce edema formation in the mouse paw [16]. This study indicates that Ang2 can alter endothelial integrity and increase vascular leakage. Fiedler et al. [17] demonstrated the crucial role of Ang2 in the induction of endothelial inflammation. Mice deficient in Ang2 cannot elicit an inflammatory response, and recombinant Ang2 restores the inflammatory defect in Ang2 (−/−) mice. Furthermore, this study demonstrated that Ang2 promoted endothelial cell adhesion molecule expression. Angiogenesis and inflammation are two tightly linked processes. The proinflammatory property of Ang2 may contribute to initial steps of angiogenesis. Because inflammation plays a key role in the development of atherosclerotic plaque formation and restenosis, the proinflammatory capacity of Ang2 may enhance atherosclerotic disease progression in patients with coronary artery disease. Therefore, the safety issue of combined Ang2 with EPCs to treat ischemic cardiovascular disease needs to be studied further.

In summary, the novel finding reported by Kim et al. [6] of proangiogenic Ang2-Tie2 signaling in EPCs contributes to a better basic understanding of the mechanism of stem cell–mediated new vessel formation. From a therapeutic point of view, if the proangiogenic activity of Ang2 can be reproduced in other types of stem cells, combining stem cells with Ang2 may provide a new ray of hope for future therapy of patients with ischemic disease not curable with conventional therapy.

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References