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Survey

The angiopoietin:Tie 2 interaction: A potential target for future therapies in human vascular disease☆

Andrew Moss *

Department of Surgery, James Paget Hospital, Lowestoft Road, Gorleston, Norfolk, England NR31 6LA, United Kingdom

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ABSTRACT

Angiopoietin-1 and -2 are endogenous ligands for the vascular endothelial receptor tyrosine kinase Tie2. Signalling by angiopoietin-1 promotes vascular endothelial cell survival and the sprouting and reorganisation of blood vessels, as well as inhibiting activation of the vascular endothelial barrier to reduce leakage and leucocyte migration into tissues. Angiopoietin-2 generally has an opposing action, and is released naturally at times of vascular growth and inflammation. There is a significant body of emerging evidence that promoting the actions of angiopoietin-1 through Tie2 is of benefit in pathologies of vascular activation, such as sepsis, stroke, diabetic retinopathy and asthma. Similarly, methods to inhibit the actions of angiopoietin-2 are emerging and have been demonstrated to be of preclinical and clinical benefit in reducing tumour angiogenesis. Here the author reviews the evidence for potential benefits of modulation of the interaction of angiopoietins with Tie2, and the potential applications. Additionally, methods for delivery of the complex protein angiopoietin-1 are discussed, as well as potentially deleterious consequences of administering angiopoietin-1.

Contents

☆ This manuscript is intended to review the preclinical and clinical settings in which modification of the signalling of angiopoietins through their receptor Tie2 have been shown to have significant potential, particularly in SIRS, the promotion of angiogenesis, and inhibiting tumour angiogenesis. Subsequently, the authors describe actual and potential delivery methods for agents modulating the activity of the angiopoietins, both in preclinical models and what is known in human models, and conclude with perspectives for future research.

* Tel.: +44 07533545781.
E-mail address: ajmossey@hotmail.co.uk

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Angiopoietin-1 (ang1) is a secreted glycoprotein ligand produced by peri-endothelial mural cells. It functions as a ligand for the receptor tyrosine kinase Tie2, the latter being found primarily on vascular endothelial cells. Besides ang1, there are three other members of the angiopoietin family, angiopoietin-2 (ang2), angiopoietin-3 and angiopoietin-4. Ang1 is an agonist at the receptor [1], whereas ang2 is a partial agonist, antagonising the response of Tie2 to ang1 [2,3].

In adult animals, whilst Tie2, in an activated state, appears to be located throughout the vasculature, together with ang1, ang2 is only released at sites of inflammation or angiogenesis. These include healing wounds and ovarian follicle growth [2,4]. The balance between quiescent and destabilised vasculature is not only important in normal processes but also in disease. Ang1 is an anti-inflammatory molecule, whereas ang2, by interfering with the former, leads to endothelial barrier destabilisation, endothelial cell activation, and vascular inflammation. This process is fundamental in many human vascular diseases, including the systemic inflammatory response syndrome (SIRS), asthma, stroke, retinopathy, nephropathy, poor diabetic wound healing, chronic cardiac allograft rejection, and radiation arteritis. This suggests that ang1 may have usefulness in therapy. Here we review current evidence and potential for this, and potential delivery methods for ang1.

1. Angiopoietins and their interaction with Tie2

1.1. Angiopoietin-1 and -2

Angiopoietins are a family of secreted oligomeric glycoproteins. Ang1 and ang2 have a similar overall structure which is illustrated schematically in Fig. 1 [2]. An N-terminal superclustering domain precedes a coiled-coil motif. Immediately downstream is a short linker, followed by a fibrinogen-related domain (FRD). The C-terminal FRD domain is composed of a further three domains, A, B and P. The P domain lies on the undersurface of the molecule and contains the Tie2 binding region [5]. The coiled-coil domain is responsible for oligomerisation of the angiopoietin monomers [6,7], whilst the superclustering domain allows the formation of higher order multimers from angiopoietin oligomers [6,8]. Angiopoietin-2 forms only a small proportion of higher order multimers, whilst ang1 is present predominantly as higher order multimers [6]. The linker domain allows secreted ang1, but not ang2, to bind the extracellular matrix [9].

The distribution of ang1 is widespread in the normal adult vascular system, mainly resulting from production by pericytes [1,10], though other cells such as neutrophils and monocytes can also generate ang1 [11]. In contrast ang2 is generally not expressed in tissues of the healthy adult mammal. It is stored in endothelial Weibel–Palade bodies, where it is capable of being released rapidly in response to stimulation [12]. Its secretion is induced at sites of inflammation and vessel remodelling. Consistent with this, ang2 expression is upregulated rapidly by a range of stimuli, including thrombin [12], histamine [12], VEGF [13], hypoxia [14] and angiotensin II [15].

1.2. Angiopoietin signalling through the Tie2 receptor

Ang1 and ang2 signal primarily through the 150 kDa transmembrane receptor tyrosine kinase Tie2 [1]. It is comprised of an extracellular domain, which binds the angiopoietins [1,2,5], a short transmembrane region, and a split intracellular tyrosine kinase domain responsible for intracellular signalling. Binding of angiopoietin clusters Tie2 molecules, with a minimum of four monomers assembles in a tetrameric conformation being required to stimulate the tyrosine kinase domains [6]. This is illustrated in Fig. 2. Tie2 is ubiquitous in the vascular endothelium. Tie2 appears to be constitutively phosphorylated in quiescent vasculature [16], indicating an active role in vascular maintenance. Tie2 is also expressed to a variable extent on nonendothelial cells, such as monocytes, synovial membrane cells, cancer cells and neurones [17–21].

The cellular consequences of ang1 signalling through Tie2 are summarised in Fig. 3. The known signalling pathways are not discussed in detail in this review, but are discussed in other works [22,23]. The cellular effects of ang1 are generally protective. The ligand inhibits endothelial apoptosis in response to a serum-deprivation and TNF-α [24], in addition to nonendothelial cells such as neurones and myocytes [25,26]. Ang1 promotes migration of endothelial and some nonendothelial cells such as smooth muscle cells [27,28]. Ang1 also induces sprouting and reorganisation of endothelial cells into tubules [29,30].

Ang1 exerts potent anti-inflammatory effects on endothelial cells, suppressing VEGF-induced upregulation of E-selectin, ICAM-1 and VCAM-1, and inhibiting leucocyte adhesion and transmigration in response to VEGF and TNF-α [31,32]. Ang1 also reduces endothelial permeability in response to VEGF and thrombin in HUVECs [32]. Ang1 stimulates the localisation to cellular junctions of proteins involved in promoting junctional integrity, such as PECAM-1 [32], occludin [33] and ZO-2 [34].

Whilst ang1 is an agonist at Tie2, ang2 is a partial agonist, with high concentrations of ang2 leading to competitive inhibition of ang1 signalling through Tie2 [3]. As ang1 and ang2 form similar

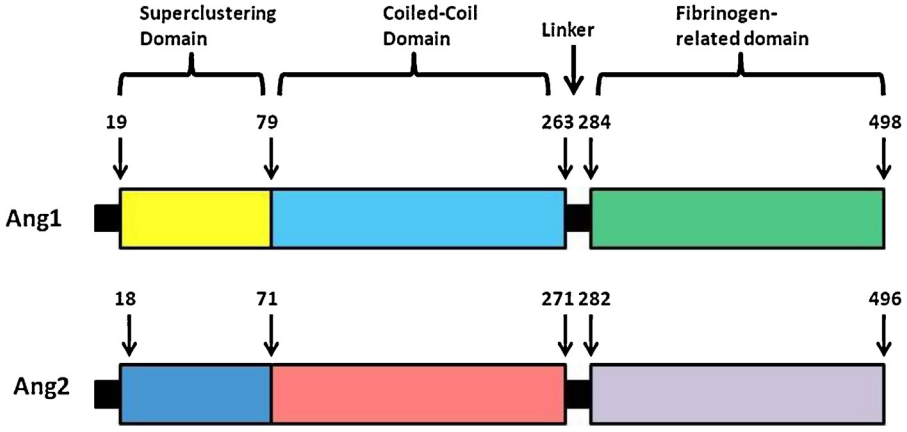

Fig. 1. Schematic diagram outlining the structure of native ang1/ang2. In each, short secretory signal sequences are followed by a superclustering domain from residues 20 to 79 and 19 to 71 in ang1/ang2 respectively. Amino acids 80–263 and 72–271 are the coiled-coil oligomerisation domains. Short linkers are then followed by residues 285–498 and 283–496 which are the fibrinogen-related receptor binding domains.

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