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COMP-Ang1: Therapeutic potential of an engineered Angiopoietin-1 variant

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ABSTRACT

The Angiopoietin-1/2 system is an opportune target for therapeutic intervention in a wide range of vascular pathologies, particularly through its association with endothelium. The complex multi-domain structure of native human Angiopoietin-1 has hindered its widespread applicability as a therapeutic agent, prompting the search for alternative approaches to mimicking the Ang1:Tie2 signalling axis; a system with highly complex patterns of regulation involving multiple structurally similar molecules. An engineered variant, Cartilage Oligomeric Matrix Protein - Angiopoietin-1 (COMP-Ang1), has been demonstrated to overcome the limitations of the native molecule and activate the Tie2 pathway with several fold greater potency than Ang1, both in vitro and in vivo. The therapeutic efficacy of COMP-Ang1, at both the vascular and systemic levels, is evident from multiple studies. Beneficial impacts on skeletal muscle regeneration, wound healing and angiogenesis have been reported alongside renoprotective, anti-hypertensive and anti-inflammatory effects. COMP-Ang1 has also demonstrated synergy with other compounds to heighten bone repair, has been leveraged for potential use as a co-therapeutic for enhanced targeted cancer treatment, and has received considerable attention as an anti-leakage agent for microvascular diseases like diabetic retinopathy. This review examines the vascular Angiopoietin:Tie2 signalling mechanism, evaluates the potential therapeutic merits of engineered COMP-Ang1 in both vascular and systemic contexts, and addresses the inherent translational challenges in moving this potential therapeutic from bench-to-bedside.

1. Introduction

The vascular system is a complex multicellular network of blood vessels spanning the entire body (excluding the cornea and outer layers of skin). Pivotal to vascular homeostasis is the endothelium that lines the lumen of all vessels, where it serves as a selective barrier regulating perfusion between the blood stream and tissues. In this respect, endothelial morphology is quite heterogeneous across the vascular tree, with highest levels of inter-endothelial junction expression located within the blood-brain and blood-retinal barriers. Dysregulation of barrier function leading to elevated vascular leakage is a common hallmark of many vascular diseases including stroke and retinopathy [1].

The endothelium is highly sensitive to change within the surrounding environment, and barrier integrity is known to be influenced by biomechanical stimuli such as shear stress and cyclic circumferential strain, as well as humoral signals such as proinflammatory cytokines and growth factors (e.g. Angiopoietins, vascular endothelial growth factor) [2]. Of particular interest to the current review, Angiopoietin-1 (Ang1) exerts a strong regulatory influence over emergent blood vessels and has been found to substantially improve vascular stability/integrity in mature vessels [3,4]. Its interaction with the endothelial-specific Tie2 receptor has received considerable attention in the literature [5,6], as has its purported therapeutic efficacy [7,8]. However, a number of disadvantages arising from the complex multi-domain structure of Ang1, have hindered its widespread applicability as a therapeutic agent, prompting the search for alternative approaches to mimicking the Ang1:Tie2 signalling axis [3,9].

The relatively recently developed engineered Ang1 variant, COMP-

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Ang1 [3], has been found to overcome the earlier limitations of Ang1, and to activate Tie2 with several fold higher potency than native Ang1, both in vitro and in vivo [10–12]. This review sets out to examine the phenomenon of Angiopoietin:Tie2 signalling in the vasculature with the specific purpose of evaluating the therapeutic benefits of engineered COMP-Ang1 within both vascular and non-vascular contexts, as well as assessing the translational challenges it faces.

2. Angiopoietin signalling and the Tie2 pathway

Angiopoietin (Ang1–4) growth factors and tyrosine kinase with immunoglobulin-like and EGF-like domains (Tie1, Tie2) receptors operate synergistically, forming receptor signalling complexes that help co-ordinate vascular endothelial morphogenesis and promote vessel stabilization (for review, see Augustin et al. [13]). The disruption of this pathway has demonstrably aberrant effects on endothelial health with serious implications for a variety of vascular disease states [14]. Here, we will specifically address Ang1/2 and Tie1/2, the most well characterised.

An examination of the molecular players involved reveals complex patterns of regulation. Following constitutive expression of Ang1 by perivascular cells, binding of endothelial Tie2 to the Ang1 ligand induces receptor phosphorylation and activation [15]. This activates the PI3K-Akt pathway culminating in downstream release of endothelial nitric oxide synthase (eNOS). This modulates vascular tone and blood flow, increases inter-endothelial junction assembly, promotes vessel survival, quiescence and maturation, and decreases endothelial inflammation [2,4,13,15–17]. In this way, Ang1 helps to co-ordinate the migration and maturation of endothelial cells in newly-formed vessels and contributes to structural stabilization in mature quiescent vessels [3]. An important step in achieving these essential functions is the rapid recruitment of Tie2 to the desired site of action, with the spatial localization of the target cell strongly influencing the resulting down-stream signalling pathway. Upon stimulation with either native Ang1 or engineered COMP-Ang1 (discussed below), rapid relocation of Tie2 from the plasma membrane to cell-cell contacts is induced (within 5 min), with sustained stimulation resulting in additional recruitment after 15–45 min. Where cells are isolated, Tie2 is instead directed by Ang1 to cell-substrate contacts, where the Erk pathway is alternatively activated [18].

Tie2 activation subsequently leads to its internalisation, causing ligand release and receptor dephosphorylation through the action of vascular endothelial protein tyrosine phosphatase (VE-PTP) [14,19]. The latter phosphatase, VE-PTP, is associated with vascular endothelial cadherin (VE-cadherin), a major component of endothelial adherens junctions [20].

Ang2 is primarily expressed at sites of elevated vascular remodelling in mice and humans and has been shown to be an important, albeit poorly understood, regulator of angiogenesis via interaction with Tie2 and integrins [21,22]. Mechanistically, Ang2 serves as a context-dependent antagonist of Ang1/Tie2 signalling, its pro-inflammatory effects in vascular endothelial cells being well documented in several disease models. Over-expression of Ang2 in the retina of diabetic mice for example, was found to significantly enhance diabetic vasoregression via pericyte dropout [23]. Naturally present in higher concentrations than Ang1, the context-specific behaviour of Ang2 may elicit some similar effects to Ang1 under certain circumstances (e.g. hypoxia, the presence of VEGF or angiotensin-II) [24,25]. Ahmed et al. [26] demonstrated using Human Umbilical Vein Endothelial Cells (HUVECs) that stimulation with Ang2 could induce concentration-dependent release of nitric oxide (NO), in a Tie2-dependent manner.

Unlike Tie2, Tie1 is regarded as an orphan receptor. It exhibits a strong degree of structural similarity to Tie2 with which it may form a heterodimeric complex (following activation of the latter by Ang1), bringing an additional layer of complexity to the Tie2 signalling pathway [27]. Tie1 has been linked with numerous pathologies, and related literature is filled with contrasting opinions on the signalling mechanisms involved. For example, Tie1 has been associated with atherosclerosis, where attenuation of Tie1 was associated with an increase in Tie2 phosphorylation and eNOS expression in murine models. There, Woo et al. [28] demonstrated that reduced Tie1 resulted in alleviated atherosclerosis progression in a dose-dependent manner, and further suggested that Tie1 may signal upstream of the Rho-associated, coiled-coil containing protein kinase (ROCK)-eNOS signalling pathway. In contrast, Korhonen et al. [29] reported that deletion of endothelial Tie1 in mice resulted in reduced Ang1/2-induced Tie2 activation (and reduced vascular remodelling), championing the hypothesis that Tie1 is a molecular switch capable of suppressing/blocking the agonist activity of Ang1/2 on Tie2. These differing observations of how Tie1 impacts Tie2-dependent signalling characterise the current state of understanding of Tie1 signalling.

Scientific literature demonstrates that although complex, Angiopoietin regulation/dysregulation underpins dynamic changes in endothelial structure and permeability through an orchestrated series of interactions. Ang1, in particular, has protective effects that offer therapeutic benefit [14,30]. In summary, it is clear that the Ang:Tie system is an opportune target for therapeutic intervention in a wide range of vascular pathologies.

3. COMP-Ang1: an engineered form of Ang1

Notwithstanding the clear therapeutic benefits of Ang1 to promote new vessel formation whilst stabilizing endothelial barrier function, its recombinant production and use in native form is not without challenges. These can largely be attributed to the complex multi-domain structure of Ang1, which includes; (i) a fibrinogen-like C-terminal domain; (ii) a central coiled-coil domain; and (iii) an N-terminal superclustering domain (see Fig. 1). The latter two domains are known to cause protein aggregation and insolubility during large-scale recombinant production, leading to considerable batch-to-batch variability in purified Ang1 activity. By substituting these domains with the short coiled-coil domain of cartilage oligomeric matrix protein (COMP), however, Cho and co-workers successfully generated a soluble, stable Ang1 variant, which they called COMP-Ang1 [3]. High level expression (>20 μg/mL) of N-terminal flag-tagged COMP-Ang1 in Chinese hamster ovary (CHO) cells was subsequently reported by Hwang et al. [31], the engineered Ang1 chimera subsequently proving several fold more potent at phosphorylating Tie2 than native Ang1 both in vitro and in vivo [3,9,31,32].

The therapeutic potential of COMP-Ang1 was subsequently highlighted in several animal studies. Radiation therapy, a traditional mainstay in cancer treatment, has lesional side effects that include apoptosis of capillary endothelial cells of the abdominal lamina propria. In this respect, Cho et al. [9] demonstrated how intravenous administration of COMP-Ang1 in irradiated mice can protect against microvascular endothelial apoptosis in the intestinal microvilli and prolong survival time. In a related study, COMP-Ang1 was also found to reduce both the radiation-induced decrease in bone marrow cellularity and the elevation in TUNEL staining following gene transfer into C57BL/6 mice [33]. The efficacy of COMP-Ang1 to improve wound healing; an impairment that is pronounced in diabetics, has also been the subject of early scrutiny. Employing the diabetic (db/db) mouse model, researchers have demonstrated how COMP-Ang1 delivery, either via tail vein injection as an adenovirus-encoded gene (Ade-COMP-Ang1) or via topical delivery of the recombinant protein, induced angiogenesis, lymphangiogenesis, and elevated blood flow leading to accelerated wound closure [34]. Adenoviral delivery of COMP-Ang1 also exhibited considerably greater potency than either Ang2, Ang3 or Ang4 in eliciting the enlargement of tracheal blood and lymphatic vessels, as well as higher numbers of lymphatic filopodia in adult mice [35].

The following sections will examine in greater detail the therapeutic benefits of COMP-Ang1 at the immediate vascular level and, by virtue of

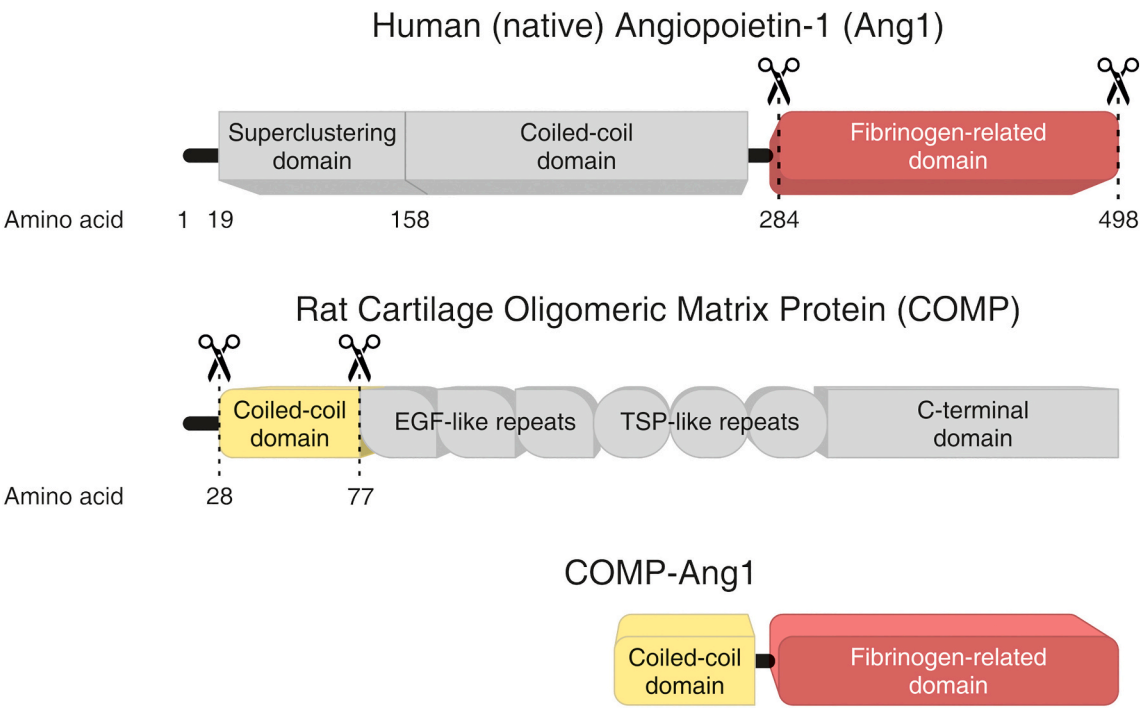

Fig. 1. Structural features of COMP-Ang-1 (bottom) formed through the fusion of the native fibrinogen-related domain (Aa284–498) of human Angiopoietin-1 to the N-terminus of the coiled-coil domain (Aa28–77) of rat COMP. (Adapted from [3,71]).

its potent vascular re-modelling capabilities, from the broader systemic perspective.

4. COMP-Ang1: vascular therapeutic benefits

Early in vivo observations with COMP-Ang1 paved the way for numerous investigations into its applicability for therapeutic angiogenesis. Using BALB/c mice, Byun et al. [36] demonstrated that donor skin grafts soaked in 50 μg/mL COMP-Ang1 (i.e. relative to Bovine Serum Albumin control) revascularized with considerably higher efficiency, a healing process that appeared to involve increased survivin expression in parallel with reduced apoptotic signalling. At 50 μg/mL, this is considerably higher than the typical 200–400 ng/mL concentration range used to induce a stabilizing effect in vitro [12,37].

Transduction of COMP-Ang1 into isolated islet cells cultured within a 3D collagen-based matrix was shown to promote their revascularization in vitro and to enhance the functionality of transplanted islet cells in vivo as reflected through improved glucose tolerance in streptozotocin-treated mice [38]. Employing a type-2 diabetic rat model, Kim et al. [39] reported enhanced angiogenesis of the penile cavernosal endothelium following injection of up to 20 μg of COMP-Ang1. The ability of COMP-Ang1 to enhance the angiogenic properties of endothelial progenitor cells (EPCs) is also evident in the improved capillary formation observed following co-incubation of treated EPCs with HUVECs in Matrigel® in vitro. In the same study, COMP-Ang1-treated EPCs also decreased infarct size in rat ischemic brain [37]. Roles for the Tie2-AKT pathway (EPC migration) and the AKT-mTOR pathway (EPC angiogenesis) were also implicated in this study. A re-engineered 'dimeric' variant of COMP-Ang1 (i.e. containing cysteine residue mutations) was also found to potently elicit angiogenesis through activation of the Tie2 pathway, with a role for N-glycosylation in its fibrinogen-like domain deemed essential for this activity [40].

As vascular leakage is a pivotal early feature of microvascular injury in various systemic pathologies, the evidence supporting COMP-Ang1's efficacy as an anti-leakage agent has seen it receive considerable attention as a treatment towards conditions such as diabetic retinopathy (see Fig. 2). A recent in vitro study by Rochfort et al. [12] comprehensively describes how COMP-Ang1 treatment of human retinal microvascular endothelial cells (HRMvECs) could substantially block the permeabilizing effects of hyperglycemia in a Tie2-dependent manner by restoring the expression of adherens and tight junction proteins responsible for regulating the paracellular pathway. Endotoxin-induced microvascular leakage in the mouse lung, heart and kidneys can also be attenuated by COMP-Ang1 treatment in-part through restoration of platelet and endothelial cell adhesion molecule-1 (PECAM-1) levels in cellular junctions [41]. The influence of endothelial crosstalk with other cell types within the microvascular unit is also relevant to the sustained beneficial effects of COMP-Ang1 in vivo during vascular challenge. Employing a murine model of *Mycoplasma pulmonis* infection, Fuxe and co-workers have shown how disruption of pericyte-endothelial crosstalk using AX102, an oligonucleotide aptamer for selective blocking of platelet-derived growth factor-B (PDGF-B), abolished the anti-leakage effects of COMP-Ang1 in tracheal vessels after 1 week [4].

COMP-Ang1 has received considerable attention as an anti-leakage agent for diabetic retinopathy (DR), the leading cause of new blindness cases in working-age people in the developed world. Notwithstanding the aforementioned HRMvEC studies by Rochfort et al. [12], Cahoon et al. [42] have shown how intravitreal injection of AAV2.COMP-Ang1 in diabetic Ins2Akita mice can significantly attenuate the main pathological hallmarks of early DR for up to 6 months. Following COMP-Ang1 gene therapy, improvements included normalization of retinal structural and functional indices such as retinal thickness and cellularity, leukocyte-endothelial interaction, retinal oxygenation and capillary density in conjunction with reduced vessel permeability. Using the same mouse model, Carroll et al. [43] also recently demonstrated how COMP-Ang1 could attenuate the increased vascular proliferation within the deep retina of aging diabetic mice, albeit without improving the neuroretinal degeneration or loss of visual acuity that accompany DR. Importantly, these findings suggest that the effects of COMP-Ang1 are temporally sensitive with respect to DR stage. Subretinal delivery of AAV2.COMP-Ang1 in a mouse model of age-related macular degeneration (AMD) has also been associated with reduced levels of vascular endothelial growth factor (VEGF), a potent endothelial permeabilizing agent, pointing to applicability as a therapeutic complement to more

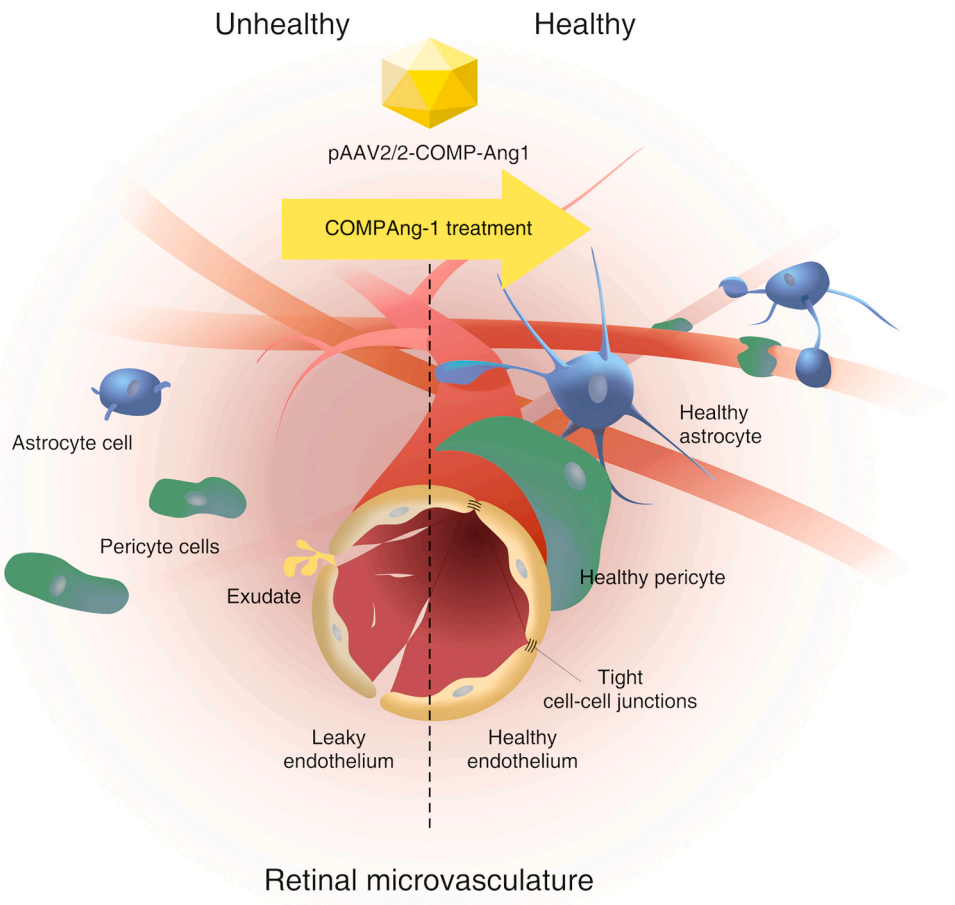

Fig. 2. Destabilization of the retinal vascular unit (manifested as endothelial permeabilization, pericyte dropout etc.) has been widely reported in diabetic retinopathy studies [23], and is believed to be attributable in-part to an increase in the Ang2/Ang1 ratio. Evidence suggests that COMP-Ang-1 delivery into the retina (e.g. intravitreal or sub-retinal injection of AAV2.COMP-Ang1) may help to normalize retinal capillary damage at specific stages of the disease [42,43].

widely used anti-VEGF strategies such as ranibizumab, bevacizumab and aflibercept (VEGF Trap-Eye) [44].

The broader vascular benefits of COMP-Ang1 have also been reported in other studies. Gene transfer of COMP-Ang1 into spontaneously hypertensive rats (SHRs) prevented systolic increases in BP as well as associated kidney and heart tissue damage [45]. The authors reported that the anti-hypertensive effects of COMP-Ang1 involved vascular endothelial Tie2 activation with downstream release of the potent

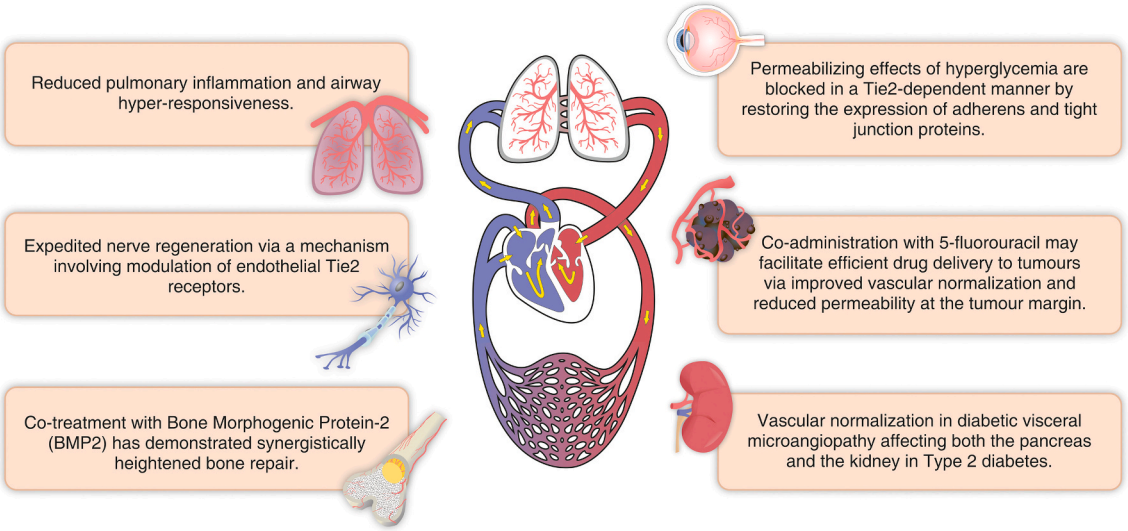

Fig. 3. COMP-Ang1 has demonstrated a range of benefits beyond the immediate vascular level, including potential as a co-therapeutic both for bone repair and as an aid in cancer treatment.

vasodilator, NO. Priming of peripheral blood stem cells with COMP-Ang1 (via the Tie2/Ets1 pathway) has also been shown to improve their neovasculogenic potential leading to their enhanced engraftment into ischemic tissue [46]. The potent anti-inflammatory properties of COMP-Ang1 have even been demonstrated to limit ischemia-reperfusion injury and allograft rejection following heart transplant in rats [47].

5. COMP-Ang1: systemic therapeutic benefits

The beneficial therapeutic effects of COMP-Ang1 extend beyond the vascular system (see Fig. 3). For example, acellular nerve grafts (ACNGs) used in the treatment of peripheral nerve defects are heavily reliant on the establishment of an efficient blood supply, with neovascularisation having been demonstrated to promote nerve regeneration [11]. In this respect, COMP-Ang1 has been demonstrated to expedite nerve regeneration via a mechanism involving modulation of endothelial Tie2 receptors [6].

The pathophysiology of various cancers is also dependent on the processes of neovascularisation and angiogenesis to supply developing tumours with requisite oxygen and nutrients. In such circumstances, the tumour microvasculature typically exhibits elevated permeability, a contributing factor to metastasis. Moreover, the chaotic nature of the tumour microvasculature ensures reduced flow effectiveness, likely hindering chemotherapy [48–50]. Hwang et al. have demonstrated that co-administration of COMP-Ang1 with 5-fluorouracil could facilitate efficient delivery of the cytotoxic drug to Lewis lung carcinoma tumours in mice [51], which the authors attributed to the ability of COMP-Ang1 to improve vascular normalization and reduce vascular permeability at the tumour margin.

Angiogenesis also plays an important role in the growth and reconstruction of bone defects dependent on the co-ordinated interplay between vessel growth and osteogenesis. In this respect, the effects of COMP-Ang1 on bone morphogenetic protein 2 (BMP2) may be leveraged by potentiating BMP2 signalling pathways [52], whilst co-treatment with COMP-Ang1 and BMP2 has been shown to synergistically heighten bone repair in a process characterised by increases in expression of endothelial- and pericyte-specific markers (i.e. PECAM-1 and NG2, respectively) [10]. In further studies, Bhattarai et al. [53] demonstrated how COMP-Ang1 resulted in mineralisation of human periodontal ligament fibroblast cells through increased expression of osteogenic transcription factors (e.g. Runx2, Osterix, and AP-1), in conjunction with increases in BMP2 and other bone-related factors.

Mature chondrocytes are essential for the formation of new bone tissue, as they are responsible for the production and maintenance of the cartilaginous matrix. To this end, they undergo terminal differentiation after they become hypertrophic, a process that involves ROS production. COMP-Ang1 has been demonstrated to accelerate chondrocyte maturation in vitro by decreasing expression of heme oxygenase-1 (HO-1), an anti-oxidative enzyme, without impacting upon BMP2 expression [54].

Despite the capacity for COMP-Ang1 to increase ROS levels within certain contexts (as shown above, for example), it has also been successfully utilised as a therapeutic agent for diseases characterised by ROS-induced inflammation, vascular leakage and plasma exudation, such as acute lung injury (ALI). In vivo investigations by Kim et al. [55] using COMP-Ang1 (administered intra-venously in PBS) suggest that it may ameliorate ALI by modulating inflammatory mediators in addition to its more familiar role of attenuating vascular leakage. In a H_2O_2-induced murine model of ALI, these authors determined that COMP-Ang1 reduced pulmonary inflammation and airway hyper-responsiveness and increased secretion of a number of inflammatory markers, including TNF-α, IL-1β, IL-4, ICAM-1, VCAM-1, and VEGF in lungs. A parallel study by Lee et al. [56] also confirmed the respiratory benefits of i.v. COMP-Ang1 therapy. Using a murine model of allergic airway disease, the authors found that COMP-Ang1 could reduce airway inflammation and hyper-responsiveness (typically manifested through increased levels of Th2 cytokines, adhesion molecules and chemokines), in-part through a reduction in lung microvascular permeability and plasma extravasation.

COMP-Ang1 is also a potentially viable therapeutic for skeletal muscle regeneration. Using COMP-Ang1-expressing adenovirus constructs, Youn et al. [57] infected injured skeletal muscle in murine models. Subsequent histological analysis clearly demonstrated improved muscle fibre regeneration in the days following treatment. Additional in vitro experiments utilising the same method of therapeutic administration found that COMP-Ang1 could regulate myogenesis via activation of transmembrane N-cadherin, which, in turn, stimulated the N-cadherin/p120-catenin/p38MAPK/myogenin pathway [57]. Importantly, COMP-Ang1 was found to bind directly to N-cadherin on the myoblast surface in a Ca^{2+}-dependent manner. Like its originator, COMP-Ang1 contains a fibrinogen-like domain on its C-terminal. Similar to fibrinogen, this domain contains multiple Ca^{2+}-binding sites, affecting calcium-dependent downstream signalling machinery.

Finally, the endothelium is naturally associated with a variety of conditions in the kidney, including renal ischemia, and tubulointerstitial fibrosis leading to unilateral ureteral obstruction. Diabetic nephropathy is a kidney-specific complication of Type-1 and Type-2 diabetes, affecting approximately 25% of diabetics, and is the main cause of end-stage renal failure [58]. Ang1-Tie2 interaction is known to influence glomeruli maturation, playing an important role in maintaining the architectural integrity of the glomerular filtration barrier. Satchell et al. [59] reported a notable decrease in podocyte (visceral glomerular epithelial cell) expression of Ang1 in the early stages of Type 1 diabetes, with a concomitant manifestation of albuminuria, nephromegaly, hyperfiltration, and structural changes to the glomerulus. Treatment with Ang1 in diabetic mice was shown to reduce albuminuria by 70% and prevented diabetes-induced glomerular endothelial cell proliferation without altering hyperfiltration or renal morphology. With respect to COMP-Ang1, Lee et al. [60] demonstrated a similar renoprotective effect using adenoviral treatment with the more stable Ang1 variant (i.e. decreased albuminuria, mesangial expansion, renal monocyte/macrophage infiltration and tubular damage/fibrosis) in db/db mice and in a cyclosporine-induced model of murine injury. Delivery of COMP-Ang1 to cyclosporine-A-treated mice markedly preserved peritubular capillary structure that was disrupted by administration of the immunosuppressant [61]. While previous experiments saw adenovirus expressing COMP-Ang1 injected into tail veins, Tian et al. [62] used localized adenoviral delivery of COMP-Ang1 to pancreatic islet capillaries and renal glomerular endothelial cells in more targeted experiments in db/db mice. The authors reported vascular normalization in diabetic visceral microangiopathy affecting both the pancreas and the kidney in Type 2 diabetes.

6. COMP-Ang1: translational challenges

The translation of any therapeutic from bench-to-bedside is a lengthy and expensive process that is fraught with challenges. Weak hypotheses, overly simplistic models with poor complementarity to the human condition, errors in data analysis, inconclusive findings, irreproducibility of results, and unfavourable drug efficacy and tolerance in patient cohorts are just some of the hurdles facing the transit of a promising therapeutic candidate along the translational continuum (for review, see Seyhan [63]).

In this respect, many questions remain to be answered before COMP-Ang1 can move towards clinical trials. Notwithstanding its obvious therapeutic efficacy in resolving diabetic vascular complications in various cell and animal models (described above), the relevance of some of these models to human pathophysiology have been widely questioned. Critiques ranging from the highly in-bred nature of some models (e.g. the Ins2Akita mouse) to background toxic effects in others (e.g. the streptozotocin-induced rat/mouse) have limited the translational power of associated findings [64,65]. Improved mechanistic data on target cell signalling effects (e.g. Tie2 and non-Tie2), optimal routes of

administration (e.g. adeno-associated virus gene transfer with potential capsid serotype variations to enhance tropism effects), the timing of COMP-Ang1 administration relative to disease stage [42,66], and dose-response characteristics across various models are all clear necessities. As Ang2 is known to rise precipitously in conditions like diabetic retinopathy, actually surpassing Ang1 levels by several fold [67,68] and contributing to cycles of inflammation and capillary destabilization, COMP-Ang1 treatment models should also be evolved to consider the benefits of incorporating an anti-Ang2 co-treatment strategy.

Finally, whilst the vast majority of published papers unsurprisingly tend to focus on the positive effects of COMP-Ang1, potential adverse effects also reflect a translational barrier and should not be ruled out. In this respect, two recent papers demonstrate how targeted administration of COMP-Ang1 by inducible transgenic expression in keratin-14-expressing cells of mice can cause excessive angiogenesis, impairing the bone marrow (BM) microenvironment and subsequently the functions of BM-derived hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), leading to abnormal hematopoiesis and erythrocyte maturation. [69,70]. Moreover, research efforts focusing on the application of COMP-Ang1 gene therapy to elicit capillary barrier tightening effects in disease states such as diabetic retinopathy should also consider the possibility that this approach may paradoxically reduce the therapeutic efficacy of endothelial progenitor cells (ECFCs) through unintended blockade of their vascular integration. [Unpublished observations, Ambati BK].

7. Summary

The engineered Ang1 variant, COMP-Ang1, exhibits a broad range of therapeutic benefits, with numerous studies showing clear evidence of downstream effects in endothelial pathways (e.g. Ang1:Tie2) mediating survival, proliferation, migration and anti-inflammatory signalling. Notwithstanding its established efficacy with respect to vascular normalization (e.g. therapeutic angiogenesis, wound healing, anti-leakage properties), the systemic nature of vasculature means that the therapeutic benefits of COMP-Ang1 may also extend to many other conditions (e.g. cancer, respiratory diseases, skeletal muscle regeneration, bone defects). Moreover, when used in combination therapy, COMP-Ang1 may synergistically heighten the effects of other therapeutic agents. While lab-based experiments to date have used a variety of delivery methods, adenoviral and adeno-associated virus-mediated delivery has been used extensively, offering a targeted means of delivering gene therapy to precise locations within the body, such as the eye or pancreatic islets. It is clear that COMP-Ang1 is a prime candidate for progression to pre-clinical trial stage in order to advance its development and realize its potential.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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