Angiopoietin-2 in sepsis: lost in translation?

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Consistent with the developmental role of angiopoietins and with the non-redundancy of the Angpt-1/Tie2 model, both, Angpt-1- and Tie2-deficient mice show complementary mid-gestational lethal phenotypes due to severe defects in angiogenesis. In line with the antagonistic actions of Angpt-1 and Angpt-2, global Angpt-2 overexpression phenocopies Angpt-1 and Tie2 deficiency, whereas Angpt-2-deficient mice have relatively mild vascular defects. However, depending on the strain (129SV or C57Bl/6 background), they die in utero or shortly after birth because of failure to grow or suffer from progressive ascites due to lymphatic defects, respectively.

In this issue of NDT, Kurniati et al. induced AKI with lipopolysaccharides (LPS) in Angpt-2 (−/−) mice and their wild-type (+/+) littermates and thoroughly analysed a putative contributory role of Angpt-2 in the development of endotoxaemic AKI [4]. Furthermore, they addressed the question of whether global genetic Angpt-2 deficiency affects not only local endothelial response to LPS in the kidney but also systemic circulating inflammatory factors. This hypothesis was based on an earlier report from Kim et al. [5] where a synthetic Angpt-1 formulation—meaning a potent Tie2 activator—was sufficient to rescue murine septic AKI.

Surprisingly, Kurniati et al. showed that Angpt-2-deficient mice are not protected from the development of septic AKI, and if anything they had even a slightly more severe AKI early on. However, less functional readouts did show potentially important findings not noticed before. Thus, endotoxic Angpt-2 (−/−) mice had less endothelial activation in the lungs and kidneys at early time-points but no differences during the later course. This could indicate that Angpt-2 might be involved in the early but not the late endothelial response to inflammatory stimuli. The group further investigated whether Angpt-2 could be a trigger for release and production of pro-inflammatory cytokines. Surprisingly, Angpt-2 (−/−) mice had higher circulating and tissue cytokine levels.

The angiopoietin (Angpt)/Tie ligand-receptor system was first identified in the mid-1990s. It consists of two transmembrane receptor tyrosine kinases, Tie1 and Tie2, and four corresponding ligands, Angpt-1−4. A functional Angpt/Tie2 system is critically important for the formation of blood and lymphatic vessels during embryogenesis. In healthy adults, its function shifts towards maintenance of endothelial homeostasis. Angpt-1 and Angpt-2 are context-dependent antagonistic ligands, which bind to the same extracellular domain of the endothelial Tie2 receptor. Angpt-1 ligation results in tyrosine phosphorylation and therefore to endothelial dysfunction, thereby forcing the cell into an apoptotic, inflammatory and anti-permeability signal transduction cascade (Figure 1) [1]. In contrary, it has been shown in vitro that excess Angpt-2 blocks Angpt-1-driven Tie2 phosphorylation, thereby forcing the cell into an apoptotic, inflammatory and hyperpermeable phenotype. A disturbed homeostasis in favour of Angpt-2 has been proposed as a culprit of many inflammatory and hyperpermeable inflammatory diseases, as it has been demonstrated in septic individuals that have high levels of circulating Angpt-2 [2]. In fact, in human sepsis, circulating Angpt-2 has demonstrated a huge potential as a biomarker of disease severity, and even as a predictor of mortality. Given the antagonistic action of Angpt-1 and Angpt-2 around their shared endothelial receptor, one might assume that excess Angpt-2 leads to Tie2 de-phosphorylation and therefore to endothelial dysfunction in vivo. Therefore, Angpt-2 could represent a promising candidate for inhibition to develop novel therapeutic strategies against sepsis-induced vascular barrier breakdown and consequently against multi-organ dysfunction. Indeed, in the Angpt/Tie2 community, it is long believed that Angpt-2 directly contributes to sepsis morbidity rather than just being a disease biomarker. These theoretical assumptions together with own data recently accepted for publication [3] suggest that Angpt-2-deficient mice (Angpt-2 −/−) should be protected from sepsis-induced acute kidney injury (AKI).
The authors state the interesting speculation that excess Angpt-2 release could actually represent a compensatory attempt at suppressing cytokine production. This fascinating theory, however, is not supported by the available data but clearly deserves thorough investigation.

In contrast to Angpt-1, little is known about the context-dependent ‘physiological’ role of Angpt-2 in mature healthy vessels. As indicated earlier, the global Angpt-2-deficient mice used here develop progressive ascites due to severe lymphatic defects. It is very possible that so far unknown (positive) effects of normal Angpt-2 baseline levels are lost in this scenario, thereby potentially worsening endotoxaemic shock. An endothelial-specific inducible Angpt-2 knockout mouse model would be a desirable tool to analyse these open questions.

In sepsis, approaches that inhibit excess circulating Angpt-2 might be more causative than strategies that exogenously activate Tie2 (e.g. with recombinant Angpt-1). But, why did an engineered variant of Angpt-1 improve septic AKI [5], but Angpt-2 deficiency did not? It is entirely possible that inhibition of a natural inhibitor (Angpt-2) could reasonably be expected to restore Tie-2 phosphorylation to pre-sepsis levels, whereas exogenous receptor activation offers greater titration control, even enabling one to exceed quiescent levels of Tie-2 activation. In fact, we have previously shown that activating Tie2 with either recombinant Angpt-1 or with an agonistic peptide ameliorates septic AKI and improves survival in murine abdominal sepsis [6, 7].

Given the number of supportive studies, we would argue that blockade of Angpt-2 is mechanistically too appealing to abandon this strategy because of a single negative report. In fact, it has been shown earlier that Angpt-2 deficiency prevents endothelial hyperpermeability and leukocyte influx in sterile peritonitis [8] as well as in hyperoxia-induced acute lung injury [9]. Even more confusingly, our own group discovered that Angpt-2 heterozygosity (very low Angpt-2 levels but absence of lymphatic defects) strongly protects against sepsis-induced multi-organ failure (including AKI) and improves survival in two different models of murine sepsis by >40% [3].

Taken together, these very recent contributions to this lively field of vascular biology research make the understanding of the Angpt/Tie2 system even more complex and raise more questions than answers. Findings by Kurniati et al. might dampen our enthusiasm in terms of pre-mature therapeutic modulation of the complex and fascinating Tie2 signalling system. In this regard, Angpt-2 driven off-target (i.e. Tie2 independent) effects, e.g. via integrin signalling, are important and may have been under-appreciated in the sepsis community [10]. To avoid disappointment, further experimental and translational research must be carried out, and Angpt/Tie2 modulation must not be introduced into the clinic prematurely. However, Angpt/Tie2 signalling is a very promising target and must not be allowed to become lost in translation.
CONFLICT OF INTEREST STATEMENT

None declared.


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Novel target in the treatment of RPGN: the activated parietal cell

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ABSTRACT

Iyoda et al. have provided strong experimental evidence for beneficial effects of PDGF signalling inhibition in two seemingly unrelated glomerular diseases: rapidly progressive glomerulonephritis (RPGN) in the present study and focal and segmental glomerulosclerosis (FSGS) in a previous study. Novel insights into the pathogenesis of these two diseases have unravelled a common cellular mechanism: activation of parietal epithelial cells (PECs). In addition, recent studies have shown that PDGF signalling is sufficient to mediate the PEC activation and formation of cellular crescents, the hallmark of RPGN. In this comment, we make an attempt to assemble the pieces of the puzzle arguing that the activated PECs might play a significant role and could represent a target for novel treatment strategies for RPGN and FSGS.

Rapidly progressive glomerulonephritis (RPGN) is characterized by proliferating cells within Bowman’s space, which typically form crescentic accumulations. RPGN is associated