Kidney calling lung and call back: how organs talk to each other

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Summary of key findings

Midkine (MK) is a retinoic acid-inducible heparin-binding growth factor involved in developmental and regeneration processes (e.g. vasculogenesis, proliferation, neurite outgrowth), but apparently also in inflammation (e.g. fibrinolysis, chemokine production, leucocyte migration) [1]. In [2] Hobo et al. show that hypertension and kidney injury that follow 5/6 nephrectomy are mediated by midkine through the activation of the renin–angiotensin system (RAS). Intriguingly, the only organ in which 5/6 nephrectomy caused upregulation of angiotensin-converting enzyme (ACE) gene and protein expression as well as enzyme activity was the lung. Midkine-deficient mice showed no upregulation of pulmonary ACE and were largely protected from hypertension and severe renal damage. Chronic administration of recombinant midkine to the MK\(^{-/-}\) mice restored hypertension and the increased pulmonary ACE expression seen after 5/6 nephrectomy. The authors provide evidence for a chain of events: the kidney communicates with the lungs via midkine; expression of ACE in lung microvascular endothelial cells is enhanced; this in turn promotes angiotensin-II-mediated hypertension and renal damage independent of the hypertension (Figure 1). These data identify midkine as a novel regulator of the RAS (at least in mice) and provide evidence for an interorgan crosstalk in the pathogenesis of angiotensin-II-mediated renal damage.

Review of the field

The lungs harbour the largest microcapillary network in the body and receive the entire cardiac output. In this central position, the lungs are designated to interact with other organs, as illustrated by the conversion of angiotensin I to angiotensin II in the lungs. This also implies that (i) agents released from injured lungs may affect distant organs, and, conversely, (ii) the lungs are prone to respond to agents released from injured extrapulmonary organs such as the kidneys (see below), liver [3], intestines [4], hind limbs [5] and pancreas [6].

(1) Lung \(\rightarrow\) kidney interactions. Ventilator-induced lung injury [7–9] offers the most studied example of lung–kidney interaction. In patients with acute kidney injury (AKI), mortality rates are 81% versus 29%, depending upon whether or not mechanical ventilation is required [10]. On the molecular level, mechanical ventilation has been shown to increase the renal expression of endothelial NO synthase [11], and to stimulate the production of endothelin [12]. High tidal volume ventilation is associated with AKI in animals [11,13] and in patients with acute lung injury [14]. Furthermore, intratracheal instillation of LPS has been reported to cause renal inflammation [15]. And also in 5/6 nephrectomy, renal damage appears to be related to pulmonary ACE expression and to lung-borne angiotensin II [2].

(2) Kidney \(\rightarrow\) lung interactions. Comprehensive studies have shown how bilateral renal ischaemia and 5/6 nephrectomy [16,17] dramatically alter pulmonary gene expression [18,19], as for example ACE [2]. Renal injury may increase pulmonary vascular permeability and downregulate ion channels critical for fluid absorption in the lungs [20] leading to pulmonary inflammation, haemorrhage, septal oedema and apoptosis within the first days [21–25], although in some studies the extent of the lung injury was weak or even absent [2,18,26].

Thus, there is ample evidence for the interaction between lungs and kidneys. However, little is known about how the information is actually transferred from one organ to the other. So far, only for sFasL [13] and angiotensin II [2] is there firm evidence of kidney damage by lung-borne mediators; vice versa, the only renal mediators strongly implicated in signalling to the lungs are IL-6 [24] and midkine [2]. These studies indicate a novel interaction between the lungs and kidneys, unrelated to blood gases, alterations in the acid–base balance, activation of the sympathetic nervous system, or regulation of blood pressure. While there is convincing evidence that the above mediators cause distant organ injury, direct evidence of their source is still lacking.
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At least three possibilities need to be considered: (i) mediators could indeed be released from specific organs. Proof of this might be obtained by measuring differences in arteriovenous concentration, examining isolated organs or by organ-specific gene manipulation. Without such evidence, the source—for example, of circulating midkine following 5/6 nephrectomy—remains unknown. Moreover, in the case of 5/6 nephrectomy, it remains to be established whether the circulating midkine or midkine from the lungs themselves induces pulmonary ACE [2]. (ii) Mediator levels might increase if one of their clearance organs is injured. This is obvious for kidneys, e.g. for IL-6 [23], but also the lungs have important clearance functions, e.g. for prostaglandins, serotonin, bradykinin or endothelin [27,28]. (iii) Injured organs might stimulate leukocytes which then act in distant organs [19], which may not necessarily be detrimental. In fact, it has been shown that acute renal injury may even protect against ventilator-induced lung injury, because uraemia attenuates pulmonary neutrophil recruitment [29].

Potential clinical implications

Communication between organs is an important factor to be considered when trying to understand the pathomechanisms of organ failure. This is a relatively understudied field and it calls for closer subspecialty interaction to achieve progress in this area. Another, relatively unresolved issue is the question whether organ interaction is purposeful, as in the case of hormones, or whether it is simply an overflow of inflammation throughout the body.

One kidney–lung communication factor may be midkine, which could represent an attractive pharmacological target. MK has been implicated in the pathogenesis of several inflammatory diseases including ischaemic nephritis, streptozotocin-induced diabetic nephropathy and neointima formation during restenosis [30–32]. In these models, MK-deficient mice showed reduced chemokine gene expression, leukocyte infiltration and lesser organ injury. MK also enhances the production of chemokines from tubular epithelial cells in culture [31,32] and, interestingly, is upregulated in hypoxaemic chronic obstructive pulmonary disease (COPD) patients [33], possibly because midkine is regulated by redox-sensitive genes such as HIF1 [34]. However, midkine has beneficial effects as well. In animal models, it was demonstrated that the growth-promoting angiogenic and anti-apoptotic properties of MK may protect neuronal cells from ischaemia [1], contribute to liver regeneration [35] and attenuate ventricular remodelling and mortality in myocardial infarction [36]. Thus, interference with midkine may be a double-edged sword.

Take-home message

The clinical lesson for nephrologists is to be aware of distal organ injury when amending kidney injury, while recognizing that other organs can also be the cause of kidney ailments, as seems to be the case in ventilator-associated lung injury [8,9] or COPD [37]. Specific treatment strategies concentrating on interorgan crosstalk need to be developed. Importantly, as is already known, the attenuation of neutrophil recruitment in uraemia may not only mitigate ventilator-induced lung injury [29], but also increase the risk of infection, in addition to having adverse effects on several distal organs [38]. In contrast, factors such as midkine may serve a more specific purpose. Just as the discovery of hormones led to novel therapies, one day, we may profit from the clinical benefits of interorgan crosstalk.

Conflict of interest statement. None declared.

References

Wnt signaling and rejuvenation of the adult kidney*

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Defects in Wnt signaling appear to underlie some forms of inherited cystic kidney disease. Knockout experiments involving the Joubier protein now examine how Wnt activity helps repair injured renal tubules in adult mice—and show that its absence leads to the formation of cysts in the mature kidney.

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