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EDITORIAL COMMENT

Hypoxia response and acute lung and kidney injury: possible implications for therapy of COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a pandemic of unprecedented severity affecting millions of people around the world and causing several hundred thousands of deaths. The presentation of the disease ranges from asymptomatic manifestations through to acute respiratory distress syndrome with the necessity of mechanical ventilation. Cytokine storm and maladaptive responses to the viral spread in the body could be responsible for the severity of disease. Many patients develop acute kidney injury (AKI) during the course of their disease, especially in more severe cases. Many factors could cause kidney damage during infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. It is still unclear whether direct viral damage or the overexpression of cytokines and inflammatory factors are preeminent. According to autoptic studies, in most of the cases, AKI is due proximal tubular damage. However, cases of collapsing focal segmental glomerulosclerosis were reported as well in the absence of signs of direct viral infection of the kidney. Considering that severe hypoxia is a hallmark of severe SARS-CoV-2 infection, the involvement of the hypoxia-inducible factor (HIF) system is very likely, possibly influencing the inflammatory response and outcome in both the lungs and kidneys. Several bodies of evidence have shown a possible role of the HIF pathway during AKI in various kidney disease models. Similar observations were made in the setting of acute lung injury. In both organs, HIF activation by means of inhibition of the prolyl-hydroxylases domain (PHD) could be protective. Considering these promising experimental data, we hypothesize that PHD inhibitors could be considered as a possible new therapy against severe SARS-CoV-2 infection.

Keywords: acute kidney injury, acute lung injury, COVID-19, focal segmental glomerulonephritis, hypoxia, hypoxia-inducible factor, PHD inhibitors, SARS-CoV-2

Coronavirus disease 2019 (COVID-19) is a pandemic of unprecedented severity threatening people and health systems all around the world; at mid-July 2020, it has already caused >500 000 deaths worldwide. The presentation of the disease ranges from asymptomatic or mild, self-limiting respiratory tract infections to severe acute respiratory distress syndrome (ARDS), with high requirements of intensive care and mortality. Cytokine storm and maladaptive responses to the viral spread in the lungs could be associated with the severity of the disease, as a possible consequence of a dysregulated host response to infection [1]. In particular, high levels of soluble interleukin (IL)-2 receptor, IL-6, IL-1, IL-10 and tumour necrosis factor-α are found in the more severe cases [2–4]. The suspicion of an overzealous immune response associated with excessive macrophage activation has been the starting point for the use of anti-cytokine therapy for dampening such exaggerated immune responses [5].

Table 1. Possible causes of AKI during SARS-CoV-2 infection

Direct viral damage to tubular cells and podocytes
Immuno-mediated damage (inflammation, cytokines and viral
  particles)
Microthrombosis
Complement activation
Hypoxia
Multiorgan failure
Dehydration and hypotension
Malnutrition
Downregulation of surface ACE2 expression
Drug toxicity
Rhabdomyolysis

Moreover, a high percentage of patients develop thrombo-embolic complications, underlining a link between inflammation and thrombosis.

COVID-19 AND ACUTE KIDNEY INJURY

In the recent months of the COVID-19 pandemic, progressive evidence has accumulated that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) hits not only the lungs, but also other organs, including the kidney. Observational data have shown a high occurrence of acute kidney injury (AKI) in patients with SARS-CoV-2 infection. According to a prospective cohort study in Wuhan, China, on admission a high percentage of patients already had urine abnormalities and/or elevated serum creatinine; during the hospitalization, AKI occurred in 5.1% of nearly 700 patients [6]. Much higher figures were reported from a data collection in the metropolitan area of New York, USA [7]. In this cohort of 5449 patients, 1993 (36.6%) developed AKI during their hospitalization (Stage 1, 46.5% ; Stage 2, 22.4%; Stage 3, 31.1%). Nearly 300 patients (14.3% of those with AKI) needed renal replacement therapy at some point. There are several possible causes of AKI in patients with SARS-CoV-2 infection (Table 1).

It is well known that the viral receptor, angiotensin-converting enzyme 2 (ACE2) protein, is expressed in the kidney in tubular proximal cells and podocytes [8]. It has been then hypothesized that AKI could be the direct consequence of the cytopathogenic effect of SARS-CoV-2 in tubular cells. Supporting this, autoptic studies showed tubular isometric vacuolization of proximal tubules on light microscopy, which correlates with double-membrane vesicles containing vacuoles seen with electronic microscopy [9, 10]. However, virus-like particles have been previously described in kidney biopsies in the absence of a viral infection. Of note, SARS-CoV-2 is not found in the urine of infected patients, even with severe disease manifestations [11, 12], except in anecdotal cases [13]. Another possible pathogenetic mechanism could be linked to the fact that the entry of SARS-CoV-2 into cells is followed by subsequent downregulation of surface ACE2 expression, causing a sharp increase in angiotensin II levels, and by impaired conversion of Ang II (into Ang 1–7), with a possible loss of its protective effects [14].

Complement activation and microthrombi formation may also have a contributory role in kidney damage, possibly with one interacting with the other [15].

Interestingly, Fanconi syndrome could precede severe AKI in many cases [16], indirectly confirming tubular damage as a major cause of AKI during SARS-CoV-2 infection.

The more severe is the clinical picture, the higher the likelihood of developing kidney failure and of having a fatal outcome [6, 17]. According to the data obtained in the metropolitan area of New York, in the majority of cases, AKI occurred coincident with severe respiratory failure requiring mechanical ventilation, with 89.7% of patients on mechanical ventilation developing AKI compared with 21.7% of non-ventilated patients [7]. Almost all the patients with AKI who required renal replacement therapy were on mechanical ventilation. These data suggest that severe hypoxia, cytokine storm or the combination of both could severely damage the kidney, not necessarily in the presence of a direct attack on the organ by the virus.

In this journal, Couturier et al. [18] recently reported on the clinical course and pathology findings for two COVID-19 patients with collapsing focal segmental glomerulosclerosis (FSGS) and severe tubulointerstitial lesions. This specific subtype of glomerulonephritis is often observed in patients affected by the human immunodeficiency virus (HIV) [19]. Other viruses, including cytomegalovirus, parvovirus B19 and Epstein–Barr virus, have been implicated as well in causing FSGS [20]. It is thought that the majority of these forms are caused by direct viral damage.

Both patients were submitted to kidney biopsy during the course of their disease because of progressively increasing proteinuria and worsening of kidney function concurrently with the worsening of lung disease and hypoxia [18]. In order to better characterize the role of SARS-CoV-2 in the development of collapsing FSGS, the authors performed reverse transcription polymerase chain reaction (RT-PCR) assay on the renal tissue specimen of one of the two patients without detecting any molecular expression of the virus. The RT-PCR assay gave negative results also in whole blood.

Interestingly, as in HIV infection, where the effect on podocytes is strongest in African American individuals with apolipoprotein L1 (APOL1) risk alleles [21], the two patients were found either homozygous for the G1 polymorphism, or heterozygous (G1/G2) [18].

This report supports an indirect effect of SARS-CoV-2 on the kidney, at least in some cases. Podocyte dysregulation and/or tubular damage might be possibly caused by the infection-driven inflammatory response that releases cytokines or viral products, together with the involvement of interferon pathways. The coexistence of hypoxia could further enhance the process and move the inflammatory response more towards maladaptation rather than tissue recovery.

THE HYPOXIA-INDUCIBLE FACTOR SYSTEM AND INFLAMMATION

Hypoxia-inducible factors (HIFs) are transcription factors orchestrating the response of the body to hypoxia. The main effectors of the system are HIF-α subunits; their availability is tightly regulated by enzymes of the prolyl-hydroxylases domain (PHD), the activity of which depends on the presence of oxygen, iron, α-ketoglutarate and ascorbic acid. Under normal oxygen conditions, HIF-α half-life is short as a consequence of hydroxylation by PHD, which marks HIF-α for proteasomal degradation; under hypoxia, PHD activity decreases, HIF-α can bind to the constitutively expressed HIF-β subunit, resulting in the activation of a large array of target hypoxia-responsive genes, promoting angiogenesis, erythropoiesis, iron availability, cell growth and migration, and a switch to a glycolytic cell metabolism. All these orchestrated activities lead to reduced cellular oxygen

consumption and increased availability of molecular oxygen in the cellular microenvironment [22].

The HIF system is critical also for inflammation and control of immune cell metabolism and function [23]. Indeed, hypoxia and inflammation are unequivocally linked, since hypoxia causes inflammation in exposed tissues and, the other way around, inflammation induces a severe hypoxic response [24]. In persons with mountain sickness, the increase of proinflammatory cytokines seems to precede the vascular leakage causing pulmonary or cerebral oedema [25]. Similar data have been obtained in animal models of low-oxygen exposure, where HIF-1α activation attenuated neutrophil transmigration [26]. Another well-known model is the ischaemia–reperfusion injury following transplantation. For instance, ischaemia of lung grafts causes the production of reactive oxygen species (ROS) by the pulmonary endothelium, which in turn induces proinflammatory mediators leading to organ injury and favouring acute rejection [27].

Interestingly, similarly to exogenous inflammation, HIF-1α can enhance the production of interferon-α and -β from bone marrow-derived dendritic cells and activate T cell, linking in this way the innate and adaptive immune system [28].

From the opposite perspective, inflamed tissues become hypoxic, as a result of reduced oxygen delivery and increased oxygen consumption from cells [23]. Depending on the tissue, the determinants of pathological hypoxia are varied. In these niches, pathological hypoxia can drive immune cell dysfunction, inflammation and a worse outcome in infection [29]. To make it even more complex, a range of immunological niches with distinct microenvironmental features can exist in a given tissue [29].

THE HIF SYSTEM AND ACUTE LUNG INJURY

ARDS and its milder form acute lung injury (ALI) are characterized by diffuse alveolar injury, lung oedema formation, neutrophil-derived inflammation and surfactant dysfunction. In these conditions, hypoventilation and hypoxia result in the activation of the HIF. Several bodies of evidence showed a possible involvement of the HIF system in the pathogenesis of ALI, with hypoxia being a possible boosting factor for inflammation [30]. In particular, the Toll-like receptor 4 (TLR4) plays a crucial role in bridging the interaction between hypoxia and inflammation [30]. This pathway is a key component of the innate immune system; it recognizes specific patterns of microbial components, called pathogen-associated molecular patterns. Its activation induces the translocation of nuclear factor-kappa B to modulate the expression of pro-inflammatory genes encoding cytokines and chemokines and co-stimulatory molecules.

According to an experimental study, either sepsis or hypoxia alone caused a small activation of TLR4 signalling. In contrast, the combination of the two had a synergistic effect on macrophagic expression of TLR4 and of downstream pro-inflammatory cytokines.

Cellular bioenergetic failure caused by mitochondrial dysfunction is another mediator of alveolar epithelial injury.

Hypoxia can also negatively affect mechanisms of recovery, since it impairs oedema reabsorption from the alveolar spaces by inhibiting the sodium channels [31]. The endothelial expression of HIF-1α is also required for vascular repair and resolution of inflammatory lung injury, as shown in a mouse model with endothelial-specific HIF-1α deletion [32].

According to recent data, HIF-1α may be also critical for viral replication in lung epithelial cells. In a cell-specific HIF-1α

knockout mouse model infected with influenza A virus, HIF-1α deficiency in alveolar-Type II epithelial cell developed more viral replication and severe lung inflammation [33]. The cellular energy stress consequent to HIF-1α deficit promoted the Adenosine monophosphate (AMP)-activated protein kinase (AMPKα) signalling, which in turn initiated autophagy, the latter promoting viral replication [33]. According to data obtained in SARS-CoV infection, hypoxia can increase the capability of viral spike proteins of SARS-CoV to trigger the conversion of B cells to macrophages, contributing to massive macrophage infiltration observed in this disease [34].

Experimental data suggest that HIF-1α activation could alleviate lung injury. An *in vitro* study showed that moderate hypoxia could down-regulate IL-6 secretion; this went together with up-regulation of HIF-1α [35]. In a rat model of ALI induced by lipopolysaccharides (LPS) combined with hypoxia, the induction of HIF-1α accumulation protected the lungs during ALI by attenuating macrophage inflammatory responses [30]. In a model of ARDS, pharmacological PHD inhibition reduced the neutrophil-mediated alveolar epithelial injury; the protective effect was exerted by HIF-1-dependent enhancement of glycolysis [36]. Similar findings were obtained with pharmacological HIF stabilization in an *in vitro* model resembling mechanical ventilation [37]. Pharmacological stabilization of HIF-1α with a PHD inhibitor was also shown effective in increasing the therapeutic capacity of mesenchymal stem cells in reducing mortality, bacterial burden, inflammation and lung injury [38]. In an endothelial cell-specific inducible knockout mouse model, the endothelial depletion of PHD2 prevented the formation of leaky vessels and oedema by regulating endothelial barrier function and protected mice from LPS-induced overwhelming inflammation and death [39].

In contrast, inappropriate activation of HIF-1α may contribute to tissue damage, promote excessive neutrophilic responses and delay inflammation resolution. The timing of HIF activation may be critical. At disease onset, it could induce a pro-inflammatory state, whereas chronic activation of the pathway would lead to dampening of the inflammatory response.

THE HIF SYSTEM AND AKI

The involvement of the HIF pathway during AKI has been shown in various kidney disease models; accordingly, much experimental evidence has accumulated in recent years proposing a protective role of HIF activation obtained with PHD inhibition on AKI.

The full understanding of all the possible pathways through which the system plays its role in AKI are still a matter of research. The known effects span from an increase in oxygen supply and adaptation to limited oxygen demand, to a regulation of inflammatory processes, a decrease in oxidative stress, an improvement of mitochondrial metabolism and reduced apoptosis. The stimulation of erythropoietin synthesis could also have a role since the hormone has protective effects on AKI [40].

Given its direct link with hypoxia, the ischaemia–reperfusion model is the most studied. Accordingly, the involvement of the HIF system has been demonstrated in several studies [41, 42]. Endothelial cells are considered important mediators of the damage following ischaemia–reperfusion. During this process they undergo activation with increased expression of adhesion molecules, causing the recruitment and activation of inflammatory cells. Recently, Rajendran *et al.* [43] investigated the effects of endothelial-specific ablation of PHD2 in a mouse model of renal ischaemia–reperfusion injury. This was found to improve

early and late damages occurring during AKI, thanks to the suppression of the expression of proinflammatory genes and recruitment of inflammatory cells in a HIF-1α-dependent manner.

In another model of renal proximal tubule cells in culture, in which ischaemia was produced by either oxygen-glucose deprivation or oxidative phosphorylation with rotenone/antimycin A, HIF-1α activation by means of PHD inhibition reduced the levels of ROS with an improvement of cell viability [44]. Moreover, it improved glycogen storage and delayed Adenosine triphosphate (ATP) depletion [44].

Mitochondrial damage has been implicated in the pathogenesis of ischaemic disease, with disruption of mitochondrial dynamics (i.e. the balance between mitochondrial fission and fusion) in ischaemic cell injury. In this context, Wei *et al.* [45] demonstrated in human patients, mice and renal tubular cells from ischaemic AKI that HIF-1α induces microRNA-668, a possible regulator of gene expression able to influence the activity of mitochondrial fusion/fission proteins, protecting cells from apoptosis. Similar findings were obtained when investigating other microRNAs [46].

Gentamicin induces AKI in nearly 20% of treated patients; it is thought that its damage is mediated by the induction of apoptosis in renal proximal tubule cells and mesangial cells. Dose- and time-dependent elevation of renal *HIF-1α* mRNA levels were reported in animal studies of gentamicin-induced nephrotoxicity [47]. In the same animal model, the activation of HIF by cobalt or dimethyloxalylglycine, *N*-(methoxyoxoacetyl)-glycine methyl ester attenuated renal dysfunction, proteinuria and structural damage through a reduction of oxidative stress, inflammation and apoptosis in renal tubular epithelial cells [48]. This could be of importance in the perspective that some of the patients with severe SARS-CoV-2 infection who are admitted to intensive care units are treated with gentamicin to prevent *Pseudomonas aeruginosa* lung colonization.

As mentioned above, in the course of SARS-CoV-2 infection, AKI is often caused by tubular damage leading to acute tubular necrosis. It has been shown that lipotoxicity could contribute to the development of AKI and HIF could promote fatty acids accumulation in cells. However, in an experimental model of transgenic mice and human primary tubular epithelial cells, differing from cyclosporin treatment, the genetic deletion and pharmacological inhibition of PHDs (and thus the activation of the HIF system) did not cause cytotoxicity [49]. On the contrary, it may possibly protect tubular cells from toxic free fatty acids by trapping them as triacylglycerides in lipid droplets [49].

Of note, not all experimental observations go in the same direction. In a murine models of ischaemia–reperfusion injury and unilateral ureteral obstruction, increased expression of HIF-1α in tubular epithelial cells was associated with activation of macrophages to promote tubulointerstitial inflammation [50]. Also, in the setting of AKI during sepsis, data are not always concordant, with some studies suggesting that pre-conditioning with chronic hypoxia could be protective against subsequent AKI [51] and others showing that reduced HIF-1α expression may attenuate sepsis-induced AKI and normalize inflammatory cytokines [52]. The opposing findings could find an explanation in the different timing and degree of activation of the HIF system.

PHD INHIBITORS: A HYPOTHESIS FOR POSSIBLE USE IN SEVERE COVID-19

Especially when developing AKI, patients with SARS-CoV-2 infection have a high rate of anaemia, often severe. Anaemia is a possible precipitating factor in the course of the disease, since in the presence of respiratory insufficiency causing hypoxaemia, it makes worse peripheral tissue ischaemia. For this reason, many patients receive blood transfusion at a given time of their disease. The pathogenesis of anaemia during SARS-CoV-2 infection has many causes. The first and most obvious one is inflammation together with functional iron deficiency. In addition to this, experimental data have shown that SARS-CoV-2 inhibits the normal metabolic pathway of haeme [53]. Indeed, one viral protein combines with porphyrin to form a complex, while others coordinately attack haem to dissociate the iron to form the porphyrin [53]. This possibly causes a decrease of functioning haemoglobin quote and the release of free toxic circulating haeme [54]. Of interest also is the observation that one facilitator for SARS-CoV-2 entrance, the Glucose Regulated Protein 78 receptor, is located into bone marrow cells. It has been hypothesized that this could possibly negatively affect the maturation and development of erythropoietic cell lines [54]. Interestingly, an elevated red blood cell distribution width, which is a possible marker of slower red blood cell production and turnover, has been associated with increased mortality in COVID-19 patients [55]. Moreover, as reported by Ehsani [56], there is a distant sequence similarity between the cytoplasmic tail of the coronavirus spike protein and the hepcidin protein, possibly contributing to dysregulated iron metabolism. This hepcidin-like activity of SARS-CoV-2 could partially explain the very high ferritin levels observed in patients with COVID-19.

PHD inhibitors are oral drugs that mimic the effect of hypoxia on the HIF system. Several molecules of this class have just finished or are undergoing Phase III clinical development for the treatment of anaemia in patients with chronic kidney disease (CKD). One molecule is approved for clinical use in China and Japan. According to preliminary data of Phase III studies, PHD inhibitors are effective in increasing or maintaining haemoglobin levels in comparison to placebo or erythropoiesis-stimulating agent (ESA) with a non-inferior safety profile [57].

Differing from currently available ESAs, PHD inhibitors increase the production of endogenous erythropoietin from the kidney or the liver; on average they correct anaemia by means of much lower levels of erythropoietin in comparison with ESAs, while avoiding sharp serological peaks. It is still unknown whether this could translate into a clinical advantage in comparison with ESA.

In addition, they influence iron metabolism by direct and indirect mechanisms, leading to a decrease in serum hepcidin and ferritin levels. Of note, similar to inflamed patients with CKD, high ferritin levels are observed in patients with severe COVID-19 [2].

Differing from ESA, they effectiveness on anaemia is maintained also in patients with signs of inflammation, indirectly confirming the link between the HIF system and inflammation.

Given the promising experimental data on the possible beneficial effect of PHD inhibition on ALI or AKI and the urge of finding new treatment approaches for patients experiencing severe lung involvement of SARS-CoV-2, we wonder whether this class of drugs could be considered as a possible new therapy against severe COVID-19. This could be given in association with tocilizumab or anakinra to amplify its effects. Pilot or randomized studies with PHD inhibitors should be considered. Considering that one molecule of the class is already in clinical use in China for the treatment of anaemia in CKD patients, it would be interesting to collect retrospectively information on whether the use of a PHD inhibitor according to its indication is

associated to a better outcome in patients with SARS-CoV-2 infection.

However, caution is needed. Indeed, patients with SARS-CoV-2 infection develop a prothrombotic state causing micro or overt systemic thrombosis; during sepsis, HIF activation could increase the expression of coagulant factors and promote thrombus formation [58]. Adequate anticoagulation is now the standard of care for SARS-CoV-2 infection; this becomes of key importance in the case of a possible use of PHD inhibitors to treat patients with SARS-CoV-2 infection. Moreover, given the complexity of the HIF system, uncertainties remain as to the right timing of PHD inhibitors to maximize their potential benefits and avoid unwanted negative effects.

CONFLICT OF INTEREST STATEMENT

REFERENCES

1. Conti P, Ronconi G, Caraffa A et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by COVID-19: anti-inflammatory strategies. J Biol Regul Homeost Agents 2020; 34: 1

2. Chen G, Wu D, Guo W et al. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. J Clin Invest 2020; 130: 2620–2629

3. McGonagle D, Sharif K, O'Regan A et al. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 2020; 19: 102537

4. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: a meta-analysis. J Med Virol 2020

5. Perricone C, Triggianese P, Bartoloni E et al. The anti-viral facet of anti-rheumatic drugs: lessons from COVID-19. J Autoimmun 2020; 111: 102468

6. Cheng Y, Luo R, Wang K et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020; 97: 829–838

7. Hirsch JS, Ng JH, Ross DW et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020; 98: 209–218

8. Zou X, Chen K, Zou J et al. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 2020; 14: 185–192

9. Su H, Yang M, Wan C et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020; 98: 219–227

10. Farkash EA, Wilson AM, Jentzen JM. Ultrastructural evidence for direct renal infection with SARS-CoV-2. J Am Soc Nephrol 2020

11. Wang W, Xu Y, Gao R et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA 2020; 323: 1843–1844

12. Wölfel R, Corman VM, Guggemos W et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020; 581: 465–469

13. Sun J, Zhu A, Li H et al. Isolation of infectious SARS-CoV-2 from urine of a COVID-19 patient. Emerg Microbes Infect 2020; 9: 991–993

14. Gheblawi M, Wang K, Viveiros A et al. Angiotensin-Converting Enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. Circ Res 2020; 126: 1456–1474

15. Noris M, Benigni A, Remuzzi G. The case of complement activation in COVID-19 multiorgan impact. Kidney Int 2020

16. Kormann R, Jacquot A, Alla A et al. Coronavirus disease 2019: acute Fanconi syndrome precedes acute kidney injury. Clin Kidney J 2020; 13: 362–370

17. Lim JH, Park SH, Jeon Y et al. Fatal outcomes of COVID-19 in patients with severe acute kidney injury. J Clin Med 2020; 9: 1718

18. Couturier A, Ferlicot S, Kévin Chevalier K et al. Indirect effects of severe acute respiratory syndrome coronavirus 2 on the kidney in coronavirus disease patients. Clin Kidney J 2020; 13: 347–353

19. Meehan SM, Kim L, Chang A. A spectrum of morphologic lesions of focal segmental glomerulosclerosis by Columbia criteria in human immunodeficiency virus infection. Virchows Arch 2012; 460: 429–435

20. Chandra P, Kopp JB. Viruses and collapsing glomerulopathy: a brief critical review. Clin Kidney J 2013; 6: 1–5

21. Kopp JB, Nelson GW, Sampath K et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol 2011; 22: 2129–2137

22. Sulser P, Pickel C, Günter J et al. HIF hydroxylase inhibitors decrease cellular oxygen consumption depending on their selectivity. FASEB J 2020; 34: 2344–2358

23. Vanderhaeghen T, Vandewalle J, Libert C. Hypoxia-inducible factors in metabolic reprogramming during sepsis. FEBS J 2020; 287: 1478–1495

24. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. N Engl J Med 2011; 364: 656–665

25. Hartmann G, Tschop M, Fischer R et al. High altitude increases circulating interleukin-6, interleukin-1 receptor antagonist and C-reactive protein. Cytokine 2000; 12: 246–252

26. Rosenberger P, Schwab JM, Mirakaj V et al. Hypoxia-inducible factor-dependent induction of netrin-1 dampens inflammation caused by hypoxia. Nat Immunol 2009; 10: 195–202

27. Chatterjee S, Nieman GF, Christie JD et al. Shear stress-related mechanosignaling with lung ischemia: lessons from basic research can inform lung transplantation. Am J Physiol Lung Cell Mol Physiol 2014; 307: L668–L680

28. Wobben R, Hüsecken Y, Lodewick C et al. Role of hypoxia inducible factor-1α for interferon synthesis in mouse dendritic cells. Biol Chem 2013; 394: 495–505

29. Taylor CT, Colgan SP. Regulation of immunity and inflammation by hypoxia in immunological niches. Nat Rev Immunol 2017; 17: 774–785

30. Wu G, Xu G, Chen DW et al. Hypoxia exacerbates inflammatory acute lung injury via the toll-like receptor 4 signaling pathway. Front Immunol 2018; 9: 1667

31. Gille T, Randrianarison-Pellan N, Goolaerts A et al. Hypoxia-induced inhibition of epithelial Na(+) channels in the lung. Role of Nedd4-2 and the ubiquitin-proteasome pathway. Am J Respir Cell Mol Biol 2014; 50: 526–537

32. Huang X, Zhang X, Zhao DX et al. Endothelial hypoxia-inducible factor-1α is required for vascular repair and

resolution of inflammatory lung injury through forkhead box protein M1. *Am J Pathol* 2019; 189: 1664–1679

33. Zhao C, Chen J, Cheng L *et al*. Deficiency of HIF-1α enhances influenza A virus replication by promoting autophagy in alveolar type II epithelial cells. *Emerg Microbes Infect* 2020; 9: 691–706

34. Chiang SF, Lin TY, Chow KC *et al*. SARS spike protein induces phenotypic conversion of human B cells to macrophage-like cells. *Mol Immunol* 2010; 47: 2575–2586

35. Shirasuna K, Shimamura N, Seno K *et al*. Moderate hypoxia down-regulates interleukin-6 secretion and TLR4 expression in human Sw.71 placental cells. *Cell Physiol Biochem* 2015; 36: 2149–2160

36. Tojo K, Tamada N, Nagamine Y *et al*. Enhancement of glycolysis by inhibition of oxygen-sensing prolyl hydroxylases protects alveolar epithelial cells from acute lung injury. *FASEB J* 2018; 32: 2258–2268

37. Eckle T, Brodsky K, Bonney M *et al*. HIF1a reduces acute lung injury by optimizing carbohydrate metabolism in the alveolar epithelium. *PLoS Biol* 2013; 11: e1001665

38. Gupta N, Nizet V. Stabilization of hypoxia-inducible factor-1 alpha augments the therapeutic capacity of bone marrow-derived mesenchymal stem cells in experimental pneumonia. *Front Med (Lausanne)* 2018; 5: 131

39. Fan Q, Mao H, Xie L *et al*. Prolyl Hydroxylase Domain-2 protein regulates lipopolysaccharide-induced vascular inflammation. *Am J Pathol* 2019; 189: 200–213

40. Kwak J, Kim JH, Jang HN *et al*. Erythropoietin ameliorates ischemia/reperfusion-induced acute kidney injury via inflammasome suppression in mice. *Int J Mol Sci* 2020; 21: 3453

41. Hill P, Shukla D, Tran MG *et al*. Inhibition of hypoxia inducible factor hydroxylases protects against renal ischemia-reperfusion injury. *J Am Soc Nephrol* 2008; 19: 39–46

42. Wang H, Liu N, Li R *et al*. Nephropreventing effect of hypoxia-inducible factor 1α in a rat model of ischaemic/reperfusion acute kidney injury. *Clin Exp Pharmacol Physiol* 2018; 45: 1076–1082

43. Rajendran G, Schonfeld MP, Tiwari R *et al*. Inhibition of endothelial PHD2 suppresses post-ischemic kidney inflammation through hypoxia-inducible factor. *J Am Soc Nephrol* 2020; 31: 501–516

44. Ito M, Tanaka T, Ishii T *et al*. Prolyl hydroxylase inhibition protects the kidneys from ischemia via upregulation of glycogen storage. *Kidney Int* 2020; 97: 687–701

45. Wei Q, Sun H, Song S *et al*. MicroRNA-668 represses MTP18 to preserve mitochondrial dynamics in ischemic acute kidney injury. *J Clin Invest* 2018; 128: 5448–5464

46. Xu X, Kriegel AJ, Liu Y *et al*. Delayed ischemic preconditioning contributes to renal protection by upregulation of miR-21. *Kidney Int* 2012; 82: 1167–1175

47. Xu EY, Perlina A, Vu H *et al*. Integrated pathway analysis of rat urine metabolic profiles and kidney transcriptomic profiles to elucidate the systems toxicology of model nephrotoxicants. *Chem Res Toxicol* 2008; 21: 1548–1561

48. Ahn JM, You SJ, Lee YM *et al*. Hypoxia-inducible factor activation protects the kidney from gentamicin-induced acute injury. *PLoS One* 2012; 7: e48952

49. Schley G, Grampp S, Goppelt-Struebe M. Inhibition of oxygen-sensing prolyl hydroxylases increases lipid accumulation in human primary tubular epithelial cells without inducing ER stress. *Cell Tissue Res* 2020; 381: 125–140

50. Li ZL, Lv LL, Tang TT *et al*. HIF-1α Inducing exosomal microRNA-23a expression mediates the cross-talk between tubular epithelial cells and macrophages in tubulointerstitial inflammation. *Kidney Int* 2019; 95: 388–404

51. Yang CC, Ma MC, Chien CT *et al*. Hypoxic preconditioning attenuates lipopolysaccharide-induced oxidative stress in rat kidneys. *J Physiol* 2007; 582: 407–419

52. Ogura Y, Jesmin S, Yamaguchi N *et al*. Potential amelioration of upregulated renal HIF-1alpha-endothelin-1 system by landiolol hydrochloride in a rat model of endotoxemia. *Life Sci* 2014; 118: 347–356

53. Wenzhong L, Hualan L. COVID-19 disease: ORF8 and surface glycoprotein inhibit heme metabolism by binding to porphyrin. *ChemRxiv* 2020

54. Cavezzi A, Troiani E, Corrao S. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. a narrative review. *Clin Pract* 2020; 10: 1271

55. Foy BH, Carlson JT, Reinertsen E *et al*. Elevated RDW is associated with increased mortality risk in COVID-19. *medRxiv* 2020

56. Ehsani S. Distant sequence similarity between hepcidin and the novel coronavirus spike glycoprotein: a potential hint at the possibility of local iron dysregulation in COVID-19. *arXiv* 2020; posted on 27 March 2020

57. Locatelli F, Del Vecchio L, De Nicola L *et al*. Are all erythropoiesis-stimulating agents created equal? *Nephrol Dial Transplant* 2020; 10.1093/ndt/gfaa034

58. Evans CE. Hypoxia and HIF activation as a possible link between sepsis and thrombosis. *Thromb J* 2019; 17: 16