Vascular Normalization to Improve Treatment of COVID-19: Lessons from Treatment of Cancer

Lance L. Munn[1], Triantafyllos Stylianopoulos[2], Natalie K. Jain[1], C. Corey Hardin[3], Melin J. Khandekar[4], and Rakesh K. Jain[1]

ABSTRACT

The dramatic impact of the COVID-19 pandemic has resulted in an "all hands on deck" approach to find new therapies to improve outcomes in this disease. In addition to causing significant respiratory pathology, infection with SARS-CoV-2 (like infection with other respiratory viruses) directly or indirectly results in abnormal vasculature, which may contribute to hypoxemia. These vascular effects cause significant morbidity and may contribute to mortality from the disease. Given that abnormal vasculature and poor oxygenation are also hallmarks of solid tumors, lessons from the treatment of cancer may help identify drugs that can be repurposed to treat COVID-19. Although the mechanisms that result in vascular abnormalities in COVID-19 are not fully understood, it is possible that there is dysregulation of many of the same angiogenic and thrombotic pathways as seen in patients with cancer. Many anticancer therapeutics, including androgen deprivation therapy (ADT) and immune checkpoint blockers (ICB), result in vascular normalization in addition to their direct effects on tumor cells. Therefore, these therapies, which have been extensively explored in clinical trials of patients with cancer, may have beneficial effects on the vasculature of patients with COVID-19. Furthermore, these drugs may have additional effects on the disease course, as some ADTs may impact viral entry, and ICBs may accelerate T-cell–mediated viral clearance. These insights from the treatment of cancer may be leveraged to abrogate the vascular pathologies found in COVID-19 and other forms of hypoxemic respiratory failure.

The COVID-19 pandemic has transformed our world, causing staggering levels of morbidity and mortality globally. Although vaccines have been developed at record pace and immunosuppressive drugs have shown benefit in patient subgroups, improving the treatment of COVID-19 will remain an important goal until population immunity is achieved. Moreover, the yearly return of seasonal influenza suggests that even widespread vaccination will not completely eliminate COVID-19. At first glance, clinical oncology has little relevance in the treatment of COVID-19. However, as we learn more about the disease, it is possible that lessons from tumor biology will offer insights into improving therapies for COVID-19.

Like SARS-CoV, SARS-CoV-2 interacts with cells using the angiotensin converting enzyme 2 (ACE2) receptor and the transmembrane serine protease 2 (TMPRSS2; refs. 1–3). Unlike SARS-CoV, the SARS-CoV-2 spike protein has a furin cleavage site which may expand its tissue tropism via the use of additional receptors, such as neuropilin-1 (NRP1). NRP1 is a cell surface protein that serves as a coreceptor for VEGF (4–6). VEGF, an angiogenic growth factor that induces vascular leakage, is elevated in patients with COVID-19 (7). The VEGF-NRP1 pathway is involved in nociception, and there is evidence that the SARS-CoV-2 spike protein can interfere with this pathway to block pain and other neuronal signals (5, 8). It is not known, however, whether SARS-CoV-2 binding to NRP1 affects VEGF signaling through VEGFR2 in endothelial cells.

The ACE2, NRP1, and TMPRSS2 proteins are expressed on multiple cell types, including endothelial cells (9), and there is evidence that the virus can infect the endothelium, both in the lungs and throughout the body (10, 11). Even if SARS-CoV-2 infection is restricted to lung epithelium, the virus can have widespread effects on vasculature by causing a systemic inflammatory state (12–14). Whether through direct infection or systemic inflammation–induced endotheliitis, COVID-19 can result in vascular damage, loss of vascular integrity, and thrombosis. The direct effects of SARS-CoV-2 on the vasculature may be a mechanism of severe disease, independent of primary respiratory infection, epithelial damage, and impaired ventilation (15–17).

COVID-19–related vascular abnormalities have some resemblance to those seen in malignant solid tumors (11, 14, 18), and multiple nonmalignant diseases (e.g., macular degeneration, schwannomas, and tuberculosis; ref. 19). Blood vessels in tumors are structurally abnormal and often hyperpermeable, having large intercellular openings in the endothelial lining (**Fig. 1**). These vascular abnormalities are caused by the overexpression of proangiogenic factors and/or underexpression of antiangiogenic factors (20). The large openings in the tumor vessel wall can cause fluid leakage to the extravascular space, compromising blood perfusion and exacerbating tissue hypoxia (21). The resulting impaired perfusion and hypoxia are two major barriers to cancer treatment: the former compromises uniform delivery of drugs and immune cells, and the latter attenuates the killing potential of tumor reactive immune cells even after they accumulate in the tumor microenvironment.

COVID-19 exhibits a number of clinical features similar to those seen in patients with cancer, including increased tissue factor activation, presence of neutrophil extracellular traps, and activated platelets (22–26). Loss of integrity of both the epithelial and endothelial components of the alveolar-capillary membrane is a primary

[1]Edwin L. Steele Laboratories, Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts. [2]Cancer Biophysics Laboratory, Department of Mechanical and Manufacturing Engineering, University of Cyprus, Nicosia, Cyprus. [3]Department of Pulmonary and Critical Care Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts. [4]Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

Corresponding Author: Rakesh K. Jain, Edwin L. Steele Laboratories, Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, 100 Blossom St, Cox-7, Boston, MA 02114. E-mail: jain@steele.mgh.harvard.edu

Clin Cancer Res 2021;27:2706–11

doi: 10.1158/1078-0432.CCR-20-4750

Translational Relevance

While vaccines are offering hope in preventing COVID-19, there remains an urgent need for rapidly deployable therapeutics for patients with established infections. Moreover, the COVID-19 pandemic has once again highlighted the lack of effective therapies for the most severe form of hypoxemic respiratory failure, the acute respiratory distress syndrome (ARDS). ARDS in general, and in COVID-19 in particular, is associated with vascular complications and life-threatening coagulopathy. We propose that some therapies currently being tested in clinical trials (androgen deprivation therapy and immunotherapies) will have the additional benefit of normalizing the vasculature and reducing thrombosis in patients with COVID-19. Thus, these drugs may have dual roles, both in modifying the course of disease, as well as preventing vascular complications of COVID-19. Combinations of these drugs, which have been extensively studied in the oncology space, could be repurposed to ameliorate the tremendous morbidity and mortality of COVID-19.

mechanism of impaired ventilation and hypoxemia in acute respiratory distress syndrome (ARDS) and COVID-19 (27). In addition, endothelial disruption and the resulting thrombosis may lead to impaired perfusion of normally ventilated lung and more extensive hypoxemia (28). Although the lung is exposed to higher levels of ambient oxygen than tumors, alveolar pO_2 levels in the setting of V/Q mismatch are lower than normal, and relative alveolar hypoxia has been linked to inflammation (29). Alveolar hypoxia may also trigger abnormal angiogenesis, ultimately increasing inflammation by allowing inflammatory cells to accumulate in larger numbers. Endothelial dysfunction may be significantly worse in patients with diabetes, obesity, and renal dysfunction (30), all conditions associated with increased mortality from COVID-19 (31).

The fact that vascular abnormalities are common in COVID-19 raises the question of whether some therapies that can improve the function of the vasculature may help control the disease. There are important gender differences in COVID-19, with men having a higher risk of developing severe disease and death compared with women (32). Although there is no evidence of androgen excess in COVID-19, TMPRSS2, an androgen-responsive serine protease, is more abundant in males in some tissues (9, 33), potentially contributing to the observed increased risk for disease severity in men. The involvement of TMPRSS2 and furin in the activity of the virus has also led to the hypothesis that inhibition of these proteases might block virus infection and inhibit systemic dissemination (e.g., NCT04353284 and NCT04583592 are testing the TMPRSS2 inhibitor, camostat mesylate, in patients with COVID-19). In addition to direct inhibition of these proteases, multiple androgen deprivation therapies (ADT) are being tested in COVID-19 clinical trials, including the androgen receptor blockers, bicalutamide (NCT04509999 and NCT04374279) and proxalutamide (NCT04446429), and the GnRH antagonist, degarelix (NCT0439771).

Interestingly, androgen withdrawal also has beneficial effects on vasculature. We have shown that castration-induced androgen withdrawal in androgen-dependent tumors (e.g., prostate cancer) can potentiate vascular normalization by suppressing the effects of androgen-dependent expression of VEGF (34).

These indirect effects of androgen deprivation on vasculature are similar to those observed when VEGF is inhibited directly. We have shown in preclinical and clinical studies that blockade of VEGF and/or other proangiogenic factors (e.g., angiopoietin-2) can transiently normalize vessels, fortifying the tumor vessel wall and reducing vascular permeability (20, 35). This, in turn, restores the functionality of the tumor vessels, increasing delivery of oxygen, drugs, and immune cells to the tumor tissue. Better vascular function improves treatment outcomes for not only multiple malignant diseases, but also for many nonmalignant diseases characterized by abnormal blood vessels (e.g., macular degeneration, schwannomas, and tuberculosis; ref. 19). Interestingly, angiopoietin-2 levels predict severity of ARDS (36), and targeting of angiopoetin-2 by mAbs improved survival in animal models of ARDS (37).

Therefore, based on lessons from cancer treatment, we propose that ADTs can have a dual benefit for patients with androgen-dependent cancers who are also infected by SARS-CoV-2, as it could enhance cancer therapy by normalizing tumor vessels, attenuate vascular leakage and, in the case of some ADT drugs such as camostat, interfere with virus propagation by reducing TMPRSS2-mediated viral entry. Together, these effects may help mitigate the severity of COVID-19. Retrospective analysis of men in the Veneto region of Italy showed that patients with prostate cancer receiving ADT had a significantly lower risk of SARS-Cov-2 infection compared with patients not receiving ADT (38), and a smaller cohort from New York showed lower rates of hospitalizations in an ADT prostate cancer cohort (39). However, this remains an open question as other cohorts have shown no effect (40). In patients with prostate cancer, the accumulating evidence regarding the potential ability of ADT to reduce SARS-CoV-2 infectivity should be considered in weighing the risks and benefits of starting or restarting ADT.

While the risks of ADT likely preclude its use in other contexts, our argument might be extended to patients with other, nonandrogen-dependent cancers by considering how SARS-CoV-2 affects the vasculature. If COVID-19 affects the vasculature directly through infection, as well as indirectly through a hyperinflammatory state, effective treatments should involve not only the inhibition of the virus activity, but also the stabilization of the vasculature throughout the body. Furthermore, with other coronaviruses, infection causes down-regulation of the viral entry receptor, ACE2 (41), which can result in increased VEGF signaling in the context of acute lung injury (42). Thus, antagonizing VEGF, indirectly via ADT for androgen-dependent tumors or directly using anti-VEGF/R agents, could decrease blood vessel leakiness, mitigating some of the damage caused by the virus-induced inflammation and improving perfusion in the vessels. This could potentially decrease thrombosis and accumulation of inflammatory cells in the lung and reduce hypoxemia by increasing perfusion (43).

Although VEGF blockade has been associated with some thromboembolic complications (44), these can often be managed with anticoagulation (42, 45–49). The relationship between VEGF inhibition and coagulation may require careful dose titration to find the optimum balance of pro- and antithrombotic effects, similar to optimizing the dose and schedule of anti-VEGF agents for cancer treatment (50). Therefore, it is possible that inhibiting VEGF, either directly or indirectly, can improve cancer therapy in androgen-independent, as well as androgen-dependent tumors by normalizing the tumor vessels, with the additional benefit of limiting the severity of COVID-19. This concept is currently being tested in a number of clinical trials using antiangiogenic therapy in patients with COVID-19 (NCT04275414, NCT04344782, NCT04305106, and NCT04511650).

To further leverage our toolbox developed for cancer research, we recently repurposed a mathematical model for cancer to simulate

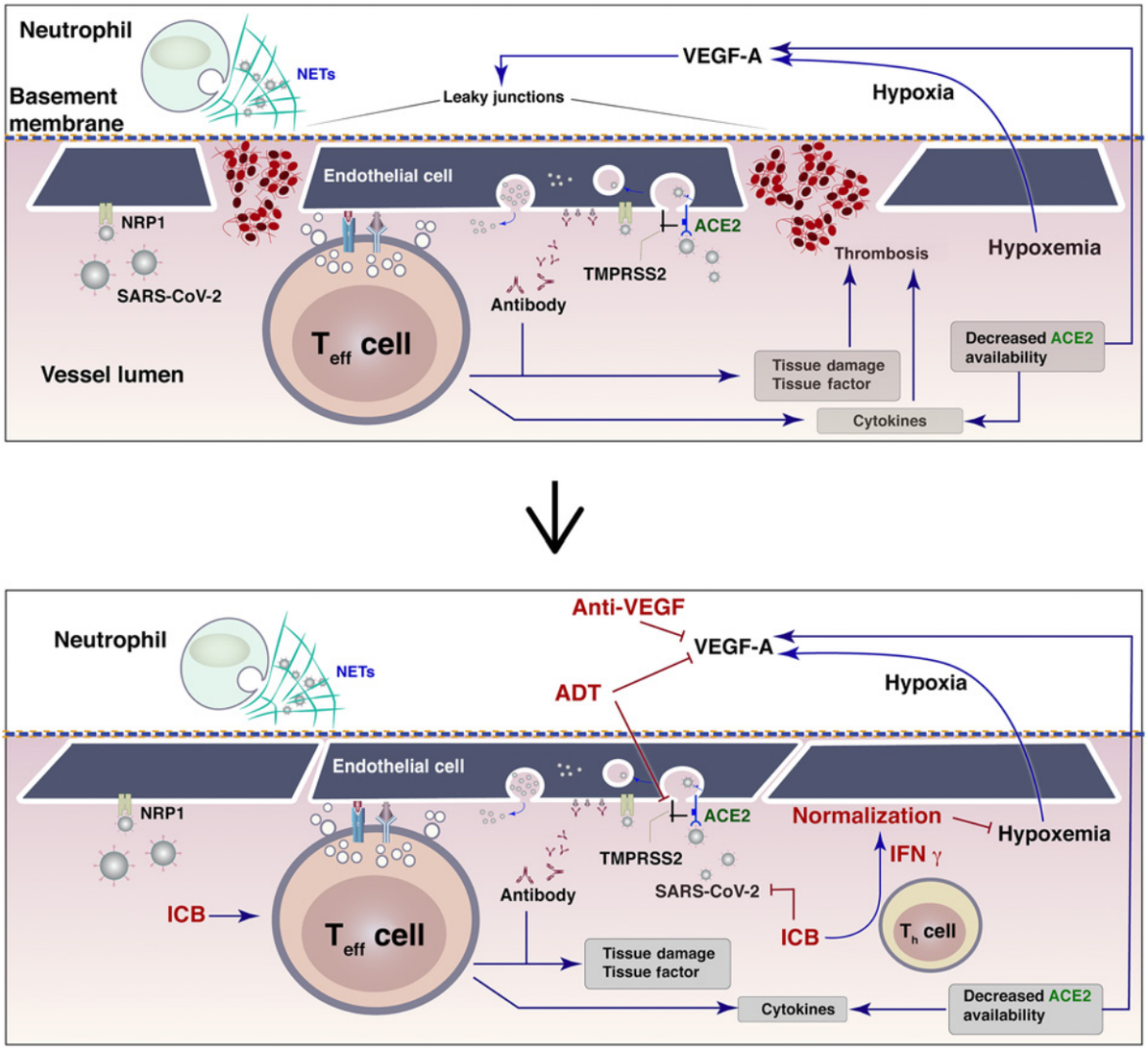

Figure 1.

Normalization of vasculature to limit thrombosis in COVID-19. Endothelial damage and vasculitis caused by viral infection, immune cell cytotoxic activity, and elevated cytokine levels can expose basement membrane and induce tissue factor and thrombosis. Sluggish blood flow, impaired ventilation, and hypoxemia can also upregulate VEGF-A, which further increases vessel leakiness and access of plasma proteins and platelets to the subendothelial matrix. We propose that ADT, in addition to affecting TMPRSS2-mediated viral entry into the cell, will help restore endothelial barrier function, thus limiting thrombosis. Furthermore, treatment with anti-VEGF drugs and/or immune checkpoint blockers in the early stage of the disease can normalize vessels and limit viral damage to the endothelium, allowing vascular repair and preventing thrombosis. NET, neutrophil extracellular trap; T_{eff} cell, effector T cell; T_h cell, helper T cell.

various COVID-19 treatment strategies. The model predicts that optimal clinical management of COVID-19 depends on the rapid response of activated effector $CD8^+$ T cells (51). In our model, early control of the virus by adaptive immunity prevents the out-of-control, self-fueling innate immune response that results in poor outcomes in some patients (51). On the basis of this finding, we propose that immune checkpoint blockers (ICB), which have revolutionized the treatment of many types of cancer, can also be employed to improve COVID-19 therapy. Indeed, it has been shown that TIM-3, a coinhibitory molecule present on T cells, is upregulated in the plasma of patients with COVID-19 (52). Furthermore, there has been interest in using ICBs in many chronic (e.g., human immunodeficiency virus and Hepatitis B and C) and acute viral diseases (e.g., influenza; ref. 53). Our simulations predict that ICBs, when given early in the disease course, can act at multiple levels against COVID-19 progression. Specifically, activation of $CD8^+$ T cells can increase the killing of virus-infected cells, which, in turn, decreases the production of proinflammatory cytokines (e.g., IL6). This model suggests that having inflammation under control, in turn, can reduce the accumulation of macrophages, neutrophils, and other cells of the innate immune system and also inhibit coagulation and blood vessel thrombosis. ICBs are also predicted to cause indirect antiviral effects by increasing production of IFN, thus limiting viral replication.

Interestingly, recent studies show that the use of ICBs for cancer therapy not only activates $CD4^+$ and $CD8^+$ T cells to elicit antitumor responses, but can also indirectly normalize the tumor vasculature by

increasing the production of IFNγ, and thus improves tumor blood vessel functionality (54–56). Therefore, similar to ADT and direct anti-VEGF drugs, it is possible that ICBs could also normalize the SARS-CoV-2–infected vessels. The timing of ICBs for treating COVID-19 must be considered carefully, however, as it is now well established that patients with severe COVID-19 benefit from immunosuppression. If given too late, that is, after the innate immune system is already ramping up, and the virus is not controlled by adaptive immunity, ICBs could exacerbate the systemic inflammatory response and worsen disease outcomes. This scenario is particularly concerning, given that ICBs can cause life-threatening pneumonitis in a small number of patients (57). In fact, initial reports suggested that ICB use was associated with more severe COVID-19 disease (58), raising concerns about immune hyperactivation. However, data from larger cohorts have been more reassuring, suggesting that there may be a complex interplay between ICB and COVID-19 disease progression (59–63). These data raise the possibility that judicious use of ICBs may be considered in some patients with COVID-19, as has been proposed in several clinical trials (e.g., NCT04356508.)

Of course, the risk–benefit analysis for ICBs is complicated by the possibility of immune-related adverse events, including myocarditis, which in some cases can be life threatening (64). Furthermore, ICBs can be associated with other rare significant immune-mediated complications (65, 66). These risks vary depending on the choice of PD-1/PD-L1 or CTLA-4 inhibitors and can be more severe with combined therapy. Given that the median time of onset of grade >3 immune-related adverse events is between 3 and 6 months (65, 66), there may be a window where a short course of ICB may be less likely to cause toxicity. Clearly, robust biomarkers for early identification of patients who are likely to develop severe disease would be essential to guide ICB therapy of patients with COVID-19.

ICBs could be combined with other therapeutics against COVID-19, such as antiviral, anti-inflammatory, and antithrombotic drugs. Indeed, the combination of antiangiogenic agents and ICBs has been shown to further improve vascular efficiency and treatment outcomes in preclinical models of cancer (67, 68), and the FDA has approved five such combinations in the past 2 years. Given the commonalities between the tumor vasculature and the blood vessels affected by SARS-CoV-2, leveraging the experience of vascular normalization in cancer may provide novel therapeutic strategies for COVID-19 (56, 69). Again, these approaches also have the potential for significant side effects and toxicity and will need to be tested in carefully designed clinical trials.

Tools that can identify patients likely to develop severe COVID-19, or more specifically, endotypes of disease with prominent vasculopathy, would help identify patients that may benefit from vascular normalization and maximize the therapeutic ratio. These patients could then be enrolled on trials of already FDA-approved drugs in the ICB, ADT, and/or VEGF pathways. We anticipate that such a collaborative effort between multiple different disciplines may yield promising new treatments for this public health crisis by repurposing drugs already approved for various malignancies. Moreover, the knowledge gained from the study of COVID-19 coagulopathy may point to therapies for other forms of ARDS, an ongoing health crisis for which there exists almost no specific therapies.

Authors' Disclosures

L.L. Munn reports grants from NIH during the conduct of the study, personal fees from Bayer, other from SimBioSys outside the submitted work, owns equity in Bayer AG, and is consultant for SimBioSys. Neither any reagent nor any funding from these organizations was used in this study. N.K. Jain and R.K. Jain report honorarium from Amgen; consultant fees from Chugai, Elpis, Merck, Ophthotech, Pfizer, SPARC, SynDevRx, and XTuit; equity in Accurius, Enlight, Ophthotech, and SynDevRx; they are members of boards of trustees of Tekla Healthcare Investors, Tekla Life Sciences Investors, Tekla Healthcare Opportunities Fund, Tekla World, and Healthcare Fund; and a grant from Boehringer Ingelheim. R.K. Jain reports NIH funding for other research projects not related to this article and has also received fees and equity from companies as an advisor/board member not related to this work. No disclosures were reported by the other authors.

Acknowledgments

R.K. Jain's research was supported by R01-CA208205 and U01-CA 224348, Outstanding Investigator award R35-CA197743, and grants from the National Foundation for Cancer Research, Jane's Trust Foundation, Advanced Medical Research Foundation, and Harvard Ludwig Cancer Center. L.L. Munn's research was supported by R01-CA2044949. T. Stylianopoulos's research was supported by the European Research Council (ERC-2019-CoG-863955).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received December 7, 2020; revised January 17, 2021; accepted February 25, 2021; published first March 1, 2021.

References

1. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;52:731–3.
2. Stopsack KH, Mucci LA, Antonarakis ES, Nelson PS, Kantoff PW. TMPRSS2 and COVID-19: serendipity or opportunity for intervention? Cancer Discov 2020;10:779–82.
3. Hoffmann M, Kleine-Weber H, Pohlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. Mol Cell 2020;78:779–84.
4. Cantuti-Castelvetri L, Ojha R, Pedro LD, Djannatian M, Franz J, Kuivanen S, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. Science 2020;370:856–60.
5. Daly JL, Simonetti B, Klein K, Chen KE, Williamson MK, Anton-Plagaro C, et al. Neuropilin-1 is a host factor for SARS-CoV-2 infection. Science 2020;370:861–5.
6. Kielian M. Enhancing host cell infection by SARS-CoV-2. Science 2020;370:765–6.
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
8. Moutal A, Martin LF, Boinon L, Gomez K, Ran D, Zhou Y, et al. SARS-CoV-2 spike protein co-opts VEGF-A/neuropilin-1 receptor signaling to induce analgesia. Pain 2021;162:243–52.
9. Gkogkou E, Barnasas G, Vougas K, Trougakos IP. Expression profiling meta-analysis of ACE2 and TMPRSS2, the putative anti-inflammatory receptor and priming protease of SARS-CoV-2 in human cells, and identification of putative modulators. Redox Biol 2020;36:101615.
10. Colmenero I, Santonja C, Alonso-Riano M, Noguera-Morel L, Hernandez-Martin A, Andina D, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. Br J Dermatol 2020;183:729–37.
11. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417–8.
12. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020;18:1023–6.

13. Chan NC, Weitz JI. COVID-19 coagulopathy, thrombosis, and bleeding. Blood 2020;136:381–3.
14. Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. Inflamm Res 2020;69:1181–9.
15. Aid M, Busman-Sahay K, Vidal SJ, Maliga Z, Bondoc S, Starke C, et al. Vascular disease and thrombosis in SARS-CoV-2-infected rhesus macaques. Cell 2020; 183:1354–66.
16. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 2020;136:489–500.
17. Escher R, Breakey N, Lammle B. Severe COVID-19 infection associated with endothelial activation. Thromb Res 2020;190:62.
18. Zunke F, Rose-John S. The shedding protease ADAM17: Physiology and pathophysiology. Biochim Biophys Acta Mol Cell Res 2017;1864:2059–70.
19. Jain RK. Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. J Clin Oncol 2013;31:2205–18.
20. Jain RK. Normalization of tumor vasculature: an emerging concept in anti-angiogenic therapy. Science 2005;307:58–62.
21. Helmlinger G, Yuan F, Dellian M, Jain RK. Interstitial pH and pO2 gradients in solid tumors *in vivo*: high-resolution measurements reveal a lack of correlation. Nat Med 1997;3:177–82.
22. Hottz ED, Azevedo-Quintanilha IG, Palhinha L, Teixeira L, Barreto EA, Pao CRR, et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. Blood 2020;136: 1330–41.
23. Manne BK, Denorme F, Middleton EA, Portier I, Rowley JW, Stubben C, et al. Platelet gene expression and function in patients with COVID-19. Blood 2020; 136:1317–29.
24. Sallah S, Wan JY, Nguyen NP, Hanrahan LR, Sigounas G. Disseminated intravascular coagulation in solid tumors: clinical and pathologic study. Thromb Haemost 2001;86:828–33.
25. Feinstein DI. Disseminated intravascular coagulation in patients with solid tumors. Oncology 2015;29:96–102.
26. Im JH, Fu W, Wang H, Bhatia SK, Hammer DA, Kowalska MA, et al. Coagulation facilitates tumor cell spreading in the pulmonary vasculature during early metastatic colony formation. Cancer Res 2004;64:8613–9.
27. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med 2017;377:1904–5.
28. Tomashefski JF Jr, Davies P, Boggis C, Greene R, Zapol WM, Reid LM. The pulmonary vascular lesions of the adult respiratory distress syndrome. Am J Pathol 1983;112:112–26.
29. Frohlich S, Boylan J, McLoughlin P. Hypoxia-induced inflammation in the lung: a potential therapeutic target in acute lung injury? Am J Respir Cell Mol Biol 2013;48:271–9.
30. Evans PC, Ed Rainger G, Mason JC, Guzik TJ, Osto E, Stamataki Z, et al. Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. Cardiovasc Res 2020;116:2177–84.
31. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430–6.
32. Klein SL, Dhakal S, Ursin RL, Deshpande S, Sandberg K, Mauvais-Jarvis F. Biological sex impacts COVID-19 outcomes. PLoS Pathog 2020;16:e1008570.
33. Cadegiani FA. Repurposing existing drugs for COVID-19: an endocrinology perspective. BMC Endocr Disord 2020;20:149.
34. Jain RK, Safabakhsh N, Sckell A, Chen Y, Jiang P, Benjamin L, et al. Endothelial cell death, angiogenesis, and microvascular function after castration in an androgen-dependent tumor: role of vascular endothelial growth factor. Proc Natl Acad Sci U S A 1998;95:10820–5.
35. Martin JD, Seano G, Jain RK. Normalizing function of tumor vessels: progress, opportunities, and challenges. Annu Rev Physiol 2019;81:505–34.
36. Calfee CS, Gallagher D, Abbott J, Thompson BT, Matthay MA, Network NA. Plasma angiopoietin-2 in clinical acute lung injury: prognostic and pathogenetic significance. Crit Care Med 2012;40:1731–7.
37. Kumpers P, Gueler F, David S, Slyke PV, Dumont DJ, Park JK, et al. The synthetic tie2 agonist peptide vasculotide protects against vascular leakage and reduces mortality in murine abdominal sepsis. Crit Care 2011;15:R261.
38. Montopoli M, Zumerle S, Vettor R, Rugge M, Zorzi M, Catapano CV, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study ($N = 4532$). Ann Oncol 2020;31: 1040–5.
39. Patel VG, Zhong X, Liaw B, Tremblay D, Tsao CK, Galsky MD, et al. Does androgen deprivation therapy protect against severe complications from COVID-19? Ann Oncol 2020;31:1419–20.
40. Klein EA, Li J, Milinovich A, Schold JD, Sharifi N, Kattan MW, et al. Androgen deprivation therapy in men with prostate cancer does not affect risk of infection with SARS-CoV-2. J Urol 2021;205:441–3.
41. Glowacka I, Bertram S, Herzog P, Pfefferle S, Steffen I, Muench MO, et al. Differential downregulation of ACE2 by the spike proteins of severe acute respiratory syndrome coronavirus and human coronavirus NL63. J Virol 2010;84:1198–205.
42. Yu X, Lin Q, Qin X, Ruan Z, Zhou J, Lin Z, et al. ACE2 antagonizes VEGFa to reduce vascular permeability during acute lung injury. Cell Physiol Biochem 2016;38:1055–62.
43. Jain RK, Finn AV, Kolodgie FD, Gold HK, Virmani R. Antiangiogenic therapy for normalization of atherosclerotic plaque vasculature: a potential strategy for plaque stabilization. Nat Clin Pract Cardiovasc Med 2007;4: 491–502.
44. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. JAMA 2008;300:2277–85.
45. Leighl NB, Bennouna J, Yi J, Moore N, Hambleton J, Hurwitz H. Bleeding events in bevacizumab-treated cancer patients who received full-dose anticoagulation and remained on study. Br J Cancer 2011;104:413–8.
46. Hurwitz HI, Saltz LB, Van Cutsem E, Cassidy J, Wiedemann J, Sirzen F, et al. Venous thromboembolic events with chemotherapy plus bevacizumab: a pooled analysis of patients in randomized phase II and III studies. J Clin Oncol 2011;29: 1757–64.
47. Komiyama S, Nagashima M, Taniguchi T, Rikitake T, Morita M. Bevacizumab plus direct oral anticoagulant therapy in ovarian cancer patients with distal deep vein thrombosis. Clin Drug Investig 2019;39:395–400.
48. Mizota A, Shitara K, Kondo C, Nomura M, Yokota T, Takahari D, et al. A case of heavily pretreated rectal cancer with disseminated intravascular coagulation that improved following reintroduction of FOLFOX plus bevacizumab. Int J Clin Oncol 2011;16:766–9.
49. Roodhart JM, Langenberg MH, Witteveen E, Voest EE. The molecular basis of class side effects due to treatment with inhibitors of the VEGF/VEGFR pathway. Curr Clin Pharmacol 2008;3:132–43.
50. Jain RK. Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia. Cancer Cell 2014;26:605–22.
51. Voutouri C, Nikmaneshi MR, Hardin CC, Patel AB, Verma A, Khandekar MJ, et al. *In silico* dynamics of COVID-19 phenotypes for optimizing clinical management. Proc Natl Acad Sci U S A 2021;118:e2021642118.
52. Ueland T, Heggelund L, Lind A, Holten AR, Tonby K, Michelsen AE, et al. Elevated plasma sTIM-3 levels in patients with severe COVID-19. J Allergy Clin Immunol 2021;147:92–8.
53. Gambichler T, Reuther J, Scheel CH, Becker JC. On the use of immune checkpoint inhibitors in patients with viral infections including COVID-19. J Immunother Cancer 2020;8:e001145.
54. Tian L, Goldstein A, Wang H, Ching Lo H, Sun Kim I, Welte T, et al. Mutual regulation of tumour vessel normalization and immunostimulatory reprogramming. Nature 2017;544:250–4.
55. Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. Nat Rev Clin Oncol 2018;15:325–40.
56. Munn LL, Jain RK. Vascular regulation of antitumor immunity. Science 2019; 365:544–5.
57. Moey MYY, Gougis P, Goldschmidt V, Johnson DB, Lebrun-Vignes B, Moslehi J, et al. Increased reporting of fatal pneumonitis associated with immune checkpoint inhibitors: a WHO pharmacovigilance database analysis. Eur Respir J 2020; 55:2000038.
58. Robilotti EV, Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M, et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med 2020;26:1218–23.
59. Luo J, Rizvi H, Egger JV, Preeshagul IR, Wolchok JD, Hellmann MD. Impact of PD-1 blockade on severity of COVID-19 in patients with lung cancers. Cancer Discov 2020;10:1121–8.
60. Lee LY, Cazier JB, Angelis V, Arnold R, Bisht V, Campton NA, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet 2020;395:1919–26.
61. Garassino MC, Whisenant JG, Huang LC, Trama A, Torri V, Agustoni F, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first

results of an international, registry-based, cohort study. Lancet Oncol 2020; 21:914–22.
62. Vivarelli S, Falzone L, Grillo CM, Scandurra G, Torino F, Libra M. Cancer management during COVID-19 pandemic: is immune checkpoint inhibitors-based immunotherapy harmful or beneficial? Cancers 2020;12:2237.
63. Maio M, Hamid O, Larkin J, Covre A, Altomonte M, Calabro L, et al. Immune checkpoint inhibitors for cancer therapy in the COVID-19 era. Clin Cancer Res 2020;26:4201–5.
64. Palaskas N, Lopez-Mattei J, Durand JB, Iliescu C, Deswal A. Immune checkpoint inhibitor myocarditis: pathophysiological characteristics, diagnosis, and treatment. J Am Heart Assoc 2020;9:e013757.
65. Tang SQ, Tang LL, Mao YP, Li WF, Chen L, Zhang Y, et al. The pattern of time to onset and resolution of immune-related adverse events caused by immune checkpoint inhibitors in cancer: a pooled analysis of 23 clinical trials and 8,436 patients. Cancer Res Treat 2020 Nov 6 [Epub ahead of print].
66. Nigro O, Pinotti G, De Galitiis F, Di Pietro FR, Giusti R, Filetti M, et al. Late immune-related adverse events in long-term responders to PD-1/PD-L1 checkpoint inhibitors: a multicentre study. Eur J Cancer 2020;134: 19–28.
67. Shigeta K, Datta M, Hato T, Kitahara S, Chen IX, Matsui A, et al. Dual programmed death receptor-1 and vascular endothelial growth factor receptor-2 blockade promotes vascular normalization and enhances antitumor immune responses in hepatocellular carcinoma. Hepatology 2020; 71:1247–61.
68. Schmittnaegel M, Rigamonti N, Kadioglu E, Cassara A, Wyser Rmili C, Kiialainen A, et al. Dual angiopoietin-2 and VEGFA inhibition elicits antitumor immunity that is enhanced by PD-1 checkpoint blockade. Sci Transl Med 2017;9: eaak9670.
69. Jain RK. Lessons from multidisciplinary translational trials on anti-angiogenic therapy of cancer. Nat Rev Cancer 2008;8:309–16.