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EDITORIAL

The rising impact of angiogenesis research

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Abstract
While inhibiting pathological angiogenesis has been long associated with the field of oncology, recent advances in angiogenesis research have impacted the progress of disease treatment for additional non-malignant diseases or chronic conditions in the fields of ophthalmology, cardiology, and gynecology. Moreover, stimulators of angiogenesis find application in ischemic diseases, while inhibitors of angiogenesis are being used to limit blood vessel formation, but in judicious ways that modify or "reprogram" the vasculature as a reinforcement for immunotherapy. We have noticed an increasing impact, as evidenced by increases in the total number of citations, in the literature surrounding the angiogenesis field suggesting that targeting angiogenesis per se is well established as a tractable approach for therapy in diverse conditions.

The year 2021 has been an excellent year for *Angiogenesis,* with again an increased submission of high impact and high-quality manuscripts. This led to a rise in the 2021 journal impact factor with almost a full point to 10.658. We, as editors of *Angiogenesis*, are determined to improve the quality of the journal, thereby serving our scientific community. As stated previously [1], we will continue to be dedicated to maintain the rigorous, fair, and fast peer-review process of submitted manuscripts and to release special issues, such as the one in 2021 on endothelial heterogeneity and plasticity [2–10]. We also aim to continue inviting reviews on trending topics in the fields of angiogenesis and vascular biology, as well as ensuring that high-quality original research articles continue to be published in *Angiogenesis*. We are grateful to the members of our editorial board and the outside reviewers for their invaluable support in selecting and improving the submitted manuscripts for publication in *Angiogenesis*. Similarly, we thank the contributing authors for their trust in the journal to submit their best and most original research.

While the last 2 years were challenging with the COVID-19 pandemic damaging almost every segment of society, it was also realized that the SARS-CoV-2-induced disease is mainly a vascular pathology [11, 12]. Therefore, not surprisingly, *Angiogenesis* received many excellent submissions on this subject. A few of these are now published and have received major attention as they are among the list of most cited papers. Smadja et al. reported on angiopoietin-2 as a marker of endothelial activation predicting serious disease and admission to the intensive care unit [13]. Angiopoietin-2 was also associated with acute kidney injury in patients with SARS-CoV-2 [14]. Another report by this group identified circulating Von Willebrand factor as a predictor of admission to intensive care and in-hospital mortality [15–17]. Also, from the multi-center MYSTIC study, COVID-19 emerged as a vascular disease. Microvascular alterations were observed in moderate to severe or critical hospitalized COVID-19 patients. Intravital microscopy and circulating levels of endothelial and glycocalyx-associated markers were observed to be modified [18].

A number of new concepts were recently presented in *Angiogenesis*. It has been described that WNT2 in colorectal cancer is elevated in cancer-associated fibroblasts. It is now shown that WNT2 has an important stimulatory role in endothelial cell migration and angiogenesis, through shifting the balance toward pro-angiogenic molecules, such as IL-6, G-CSF, and PGF. Knockdown of WNT2 was shown to suppress angiogenesis [19]. In another study, it was shown that decylubiquinone, a coenzyme Q_{10} analog, inhibits angiogenesis in breast cancer. Although it is exclusively approved by the FDA as a dietary or cosmetic supplement, it may

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be developed further as an angiogenesis inhibitor for breast cancer [20].

Angiogenesis also provides a forum for presentation of novel methods or techniques. Detter et al. described a model of cerebral cavernous malformations (CCMs), vascular lesions that are characterized by enlarged and irregular small blood vessels in the brain. By deletion of the *Ccm3* gene in the brain vasculature, and by injection of lipopolysaccharide, a valuable model for studying both pharmacological treatment of CCMs and chronic hemorrhage is presented [21]. Another study showed the efficient delivery of a microRNA (miR-92a) by deoxycholic acid-modified polyethylenimine polymeric conjugates to locally induce angiogenesis in ischemic disease [22].

Angiogenesis is also a platform for educational reviews. The most appreciated ones are mentioned herein: A review by Wang et al. reported on the role of mitochondria in cardiac microvascular ischemia–reperfusion injury. This study discusses the important role of mitochondrial reactive oxygen species in endothelial senescence and apoptosis, as well as mitochondrial dynamics such as fission, fusion, and mitophagy [23]. A comprehensive invited review was published on high endothelial venules (HEVs), specialized blood vessels maintaining leukocyte recirculation. HEVs are common in secondary lymphoid organs, such as lymph nodes, but are also observed at places of chronic inflammation, such as rheumatoid arthritis, Crohn's disease, asthma, and cancer. Tumor-associated HEVs are proposed to play a role in leukocyte entry into tumors, a process of key importance in anti-tumor immunity and a variety of cancer immunotherapies [24]. Three reviews dealing with endothelial differentiation and heterogeneity are also worth mentioning [25–27].

We highly encourage researchers to submit their exciting research to *Angiogenesis* and communicate new ideas for invited reviews and special issues to further improve the journal.

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