FOREWORD

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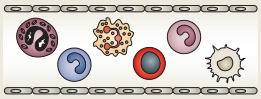

Limiting supply

Abstract | The use of agents that modulate tumour angiogenesis has led to improvements in patient care, and tumour angiogenesis remains an important area for cancer research. As more anti-angiogenic agents proceed through clinical development, it is important to consider what we now know about the effects these agents have on the tumour vasculature and what aspects of tumour angiogenesis remain to be elucidated.

Bevacizumab, an antibody that targets the pro-angiogenic factor vascular endothelial growth factor (VEGF), was the first anti-angiogenic agent to be approved for use in patients with cancer and has since been followed by other agents that target VEGF or its receptors (VEGFRs). In the United States, for example, the tyrosine kinase inhibitors (TKIs) sunitinib and sorafenib, which target VEGFRs and other closely related receptor tyrosine kinases, are approved for use as single agents for patients with renal cell carcinoma. In addition, bevacizumab is approved for use in combination with chemotherapy for patients with advanced breast, colorectal or non-small-cell lung cancer. However, although such advances are welcome, the actual benefit to patients can be relatively small.

Results from clinical trials have shown that not all patients benefit from the addition of an anti-angiogenic agent to standard chemotherapy regimens. This is reflected in some negative trial results with some anti-angiogenic agents and the modest but statistically significant improvement in survival for patients with advanced breast or colorectal cancer conferred by the addition of bevacizumab. However, a few patients show huge benefit. These findings underscore the need for accurate biomarkers that help predict which patients with cancer will respond to anti-angiogenic agents. The ability to identify this 'responder' population makes both ethical and economic sense: most anti-angiogenic drugs are expensive and this currently restricts their use in countries, like the United Kingdom, that have a national health care system. In other countries, expense limits their use to those who can afford them, but these patients are paying for a drug that might have little effect and might produce significant side effects, two further reasons for determining who will benefit most.

Predictive biomarkers are most likely to come from an improved understanding of the mechanisms that enable tumour angiogenesis and the effects that anti-angiogenic agents have on these mechanisms. However, it is still unclear how these agents affect tumour growth. As Lee Ellis and Daniel Hicklin discuss, VEGF-targeted agents can affect both endothelial cells in tumour blood vessels and other cells within the tumour that are dependent on VEGF for activation, growth and survival. The TKIs almost certainly have more widespread effects owing to their ability to target receptor tyrosine kinases other than the VEGFRs, but how much of this multi-target effect is responsible for their efficacy is unknown. One aspect, however, is abundantly clear in both preclinical models and in patients: the effect of anti-angiogenic agents is transitory. Resistance appears to develop through several mechanisms, including adaptive and intrinsic responses, as outlined by Gabriele Bergers and Douglas Hanahan. We need to develop therapeutic strategies that overcome these novel resistance mechanisms. What combinations or sequences of drugs might overcome this, and what might be the next good targets?

Our increasing understanding of the proteins involved in mediating angiogenesis and supporting the vasculature is helping to identify new targets. Integrins have many vital cellular functions and are important for both angiogenesis and lymphangiogenesis. Judith Varner and colleagues highlight the progress that has been made in understanding the complex contribution that integrins bring to the normal and tumour vasculature and indicate potential therapeutic avenues. The semaphorins are another family of proteins that regulate angiogenesis. As Gera Neufeld and Ofra Kessler discuss, semaphorins can both induce or suppress tumour angiogenesis, and we need to understand fully the downstream signalling pathways that are activated by these proteins so that we can consider how to target them therapeutically. Bone marrow-derived myeloid cells, such as macrophages and neutrophils, also have key functions in promoting tumour angiogenesis. Once again the picture is complex but, as Claire Lewis and colleagues indicate, evidence from preclinical models has identified some potential therapeutic targets.

So, there is much still to learn about tumour angiogenesis both at the bench and at the bedside but, as is shown by the content of the Reviews in this issue, targeting the tumour vasculature remains a valid therapeutic avenue with an increasing list of tools to use in the war against cancer.