Tumor Angiogenesis: A Key Target for Cancer Therapy

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For a long time progress in cancer therapy occurred in very small steps only. However, with increasing knowledge of the mechanisms and molecules involved in tumor development, this changed considerably over the last 20 years.

In the early 1990s targeted therapies have successfully been developed. Targets shown to be involved in the progression of tumors were identified and validated. Consequently, drugs were developed that were shown to interfere with the activity of such targets and to be clinically effective.

Tumor angiogenesis has been hypothesized to be a valid target for the treatment of many solid tumors and in particular their metastases. The idea was intriguing because most solid tumors and metastases are pervaded by newly formed blood vessels. Since Judah Folkman [1] had proposed this concept almost 5 decades ago, numerous attempts have been undertaken to establish anti-angiogenics as rational components for improving the so far still unsatisfactory treatment modalities.

However, after many years of exploring anti-angiogenic drugs against various types of tumors, there are two main conclusions emerging from the results: *First*, anti-angiogenic drugs alone do not keep the promises we all had hoped they would. *Second*, in most cases a positive effect could be observed only when they are given in combination with cytotoxic drugs or targeted molecules.

Tumor angiogenesis is essentially initiated by the tumor itself. As soon as the malignancy grows to a certain size it becomes hypoxic and starts to secrete angiogenic growth factor molecules. These growth factors bind to receptors on endothelial cells of nearby blood vessels and thus initiate the formation of new vessels which penetrate the tumor and support its increased growth. The most important angiogenic growth factor, secreted by the tumor cells is the vascular endothelial growth factor (VEGF). As VEGF acts predominantly on endothelial cells, it has been considered very early on as an ideal target for therapy. Bevacizumab, a humanized monoclonal antibody against VEGF-A, has been developed in the 1980s by Napoleone Ferrara, a pioneer in the angiogenesis field. As it looks now, about 3 decades later, bevacizumab is a very successful, if not the most successful, drug in clinical use.

Besides antibodies against VEGF, that interfere with VEGF to block the angiogenic signaling chain, several other strategies have been developed to interfere with VEGF signal transduction: *First*, tyrosine kinase inhibitors of the endothelial VEGF-receptors *Second*, antibodies against the VEGF receptors. *Third*, fusion proteins harboring the high-affinity binding domain of the VEGF-receptor.

In this series of reviews we have tried to exemplify the use of anti-angiogenics in the treatment of several tumor types. Furthermore, we will give an overview on the current status of FDA approved anti-angiogenic antibodies, fusion proteins and tyrosine kinase inhibitors.

In their article on 'anti-angiogenics: current situation and future perspectives', Zirlik and Duyster [2] summarize the multiple use of the different classes of drugs, so far approved for clinical use. They also give an outlook on the possibilities of combining anti-angiogenics with immune checkpoint inhibition, a promising new approach. Janning and Loges [3] focus on the use of anti-angiogenics in the treatment of non-small cell lung cancer (NSCLC). Here again the combination with immune checkpoint inhibition is discussed and a promising outlook for this tumor entity is given. Seeber, Gonsilius, Gastl and Pircher [4] summarize the value of anti-angiogenics in the therapy of metastatic colorectal cancer (mCRC). However, as the authors point out, the efficacy of and long-term response to anti-angiogenics are limited. In particular they discuss the need of validated biomarkers for improving the use of these types of drugs.

In their article on 'anti-angiogenics: their role in the treatment of glioblastoma' Winkler, Osswald and Wick [5] demonstrate that only bevacizumab has shown a meaningful efficacy in controlled clinical trials in glioblastoma so far. They also stress the need of biomarkers for the proper selection of patients.

All together these reviews show the potential and the limitations of the use of anti-angiogenics. They also show the need to further explore other angiogenic systems, such as angiopoietin/angiopoietin-receptors, for their possible use as novel anti-angiogenic targets.

Disclosure Statement

The author declares no conflicts of interest.

References

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