

# **ANGIOGENESIS: WHAT WE KNOW, WHAT WE DO NOT UNDERSTAND YET, AND WHAT WE HAVE TO DO**

**Marius Raica<sup>1</sup>**

<sup>1</sup>Victor Babes University of Medicine and Pharmacy, Department of Microscopic Morphology/Histology, Angiogenesis Research Center Timisoara, Romania

Angiogenesis is a basic process in the development of normal tissues and organs. Excessive and insufficient angiogenesis is directly involved in maintaining and development of some severe diseases. Maybe the best known example of excessive angiogenesis is the tumor-associated formation of new blood vessels that on one hand provide nutrients for cancer cells, and on the other gives rise to a network that allow the spreading of malignant cells, as Judah Folkman has shown in experimental models five decades ago [1]. The hypothesis that newly formed blood vessels are essential for tumor progression and metastasis has been hardly accepted in a period where almost only tumor cells were investigated and considered as target for therapy. The discovery and characterization of the first and most powerful angiogenic factor [2], as well as of the first antiangiogenic drug [3] dramatically changed our perspective on angiogenesis and antiangiogenesis. Since these moments, a lot of researches focused on angiogenesis as a potential prognostic factor in human tumors and as a target for therapy. Destroying and/or normalizing the vascular network it was hoped to reduce tumor dimensions and to inhibit local and regional spreading [4].

Methods to investigate and evaluate angiogenesis are very different, and even the same method applied by different groups gave controversial results. One example is microvessel density, performed virtually by almost all researchers in the field. Since 1990's when Weidner [5] described the best known and most applied method to evaluate microvessel density, its prognostic value has been demonstrated in almost all human malignant tumors. Even so, the values published by different groups are significantly different, including the works based on microscopic image analysis. The same conclusion applies to other clinico-pathologic and experimental methods used to investigate tumor-associated angiogenesis. This is why standard procedures and guidelines to apply and to interpret technical methods is not necessary, but mandatory, and it has been recently published in the journal *Angiogenesis* [6]. This is a major achievement as validation of different antiangiogenic drugs became already a necessity.

What do we know nowadays? We know that the vascular network is crucial for tumor progression, tumor-associated blood vessels are different in structure

and function from vessels found in normal tissues, and endothelial cells show a high rate of proliferation. This process is governed by growth factors, namely vascular endothelial growth factors (VEGF), platelet-derived growth factors (PDGF), fibroblast growth factors (FGF), and their cognate receptors. To the promotion and development of angiogenesis also contribute other growth factors and substances that are less investigated or their effect(s) is not enough demonstrated. It is supposed that growth factors act together at the same time or in cascade to induce formation of new blood vessels. What we do not know? We do not know why in some advanced stage malignant tumors there is a low expression of growth factors and their receptor, although they show a rich vascular supply. It is not known why in some tumors blood vessel mature quickly, and intermediate and immature vessels represent only a minority. Most probably the answer could be given by other growth factor or angiogenic substances that wait to be discovered. We need a better characterization of endothelial cells from tumor-associated blood vessels, including tip cells [6]. Otherwise, a targeted antivasular therapy without damaging normal vessels would be not possible.

A major revolution in antiangiogenic therapy was the approval in 2004 of bevacizumab by Food and Drug Administration, for patients with metastatic colorectal carcinoma [7]. The approval was based on excellent and promising results obtained in both in vitro and in vivo experiments. From that moment, there were produced a lot of humanized monoclonal antibodies, which targeted growth factors, their receptors, additional molecules, a.o. We know that in some patients bevacizumab significantly improves disease-free survival and overall survival in combination with chemotherapy. On the other hand, clinical results are far to be spectacular as initially believed. Why the failure of antiangiogenic therapy? Maybe some tumors do not express the targeted growth factor..., maybe tyrosine kinase inhibitors did not "match" with the chemotherapeutic regimen..., and maybe patients were not stratified according to the angiogenic molecular profile...

What we do not know and we should? Most probably to evaluate the effects of antivasular in addition to the antiangiogenic therapy. This should be performed in patients with angiogenic tumors, characterized

predominantly by immature and intermediate vessels with endothelium characterized by a high rate of proliferation, associated to VEGF/PDGF/FGF expression at protein level by tumor cells. Although Jimmy, a child in 1991, when he was treated by Folkman with the first antiangiogenic drug for a massive hemangioma [3], was a therapeutic success. Nowadays, it seems that we are not sure which the real place of antiangiogenic therapy is in the anti-cancer therapeutic strategy. It is not clear if a single antiangiogenic drug against a single or multiple target(s) could be the therapeutic option. How to combine antiangiogenic drugs with chemotherapy to obtain better results? These are questions that still wait an answer. We really hope the next coming researches, including those from this journal, will bring new insights of basic mechanisms of angiogenesis and antiangiogenesis in order to understand how to use them in clinical practice.

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