The Era of Angiogenesis

In a seminal publication by Dr. Judah Folkman (1), the concept of tumor angiogenesis via the identification of a then undefined tumor angiogenesis factor transformed oncology research and drug development by redirecting efforts towards a new horizon, where novel angiogenesis inhibitors held promise in the fight against cancer.

Dr. Judah Folkman is heralded as the “Father of Angiogenesis,” yet he was not the first to recognize the abnormal angiogenesis process in tumors. In a review by Stephenson and colleagues (2), we are reminded of the scientific notables from the 1700s to the early 1900s who observed vascularization in tumors and under proangiogenic experimental conditions. However, the 1974 publication (1) and subsequent exploration by Dr. Folkman and his colleagues in the period of booming biotechnology resulted in a cascade of research, which led to a deeper understanding of the multicellular nature of tumor biology.

The hypothesis of tumor dormancy and of the vascular requirement to fuel tumor growth beyond a few millimeters via an “angiogenic switch” was supported by the results of several key experiments:

- avascular growth of a tumor in an isolated, perfused organ but that rapidly grew when the tumor was transplanted into the host animal;
- dormant tumors in the anterior chamber of the rabbit eye that rapidly grew when placed against the iris;
- tumor spheroids unable to reach a size greater than a mean diameter of 2–3 mm in culture;
- tumor development in the chorioallantoic membrane after capillaries penetrated the tumor nodule.

These assays may appear rather elementary and unsophisticated compared to today’s genetic engineering, molecular profiling, and in vivo imaging modalities. However, these results significantly impacted preclinical and clinical research to follow.

Dr. Folkman championed the concept that host tissue impacts the tumor microenvironment and subsequent malignancy through the development of blood vessels. The discovery of the VEGF (3, 4), VEGF family (VEGF-A, -B, -C, -D, PI GF-1, and -2), associated isoforms, ligands, and VEGF receptors (VEGFR) rapidly ensued. The lymphangiogenesis process was uncovered. The importance of tumor hypoxia and influence on therapeutic resistance become increasingly apparent (5). Pericytes, fibroblasts, endothelial progenitor cells, and cells of hematopoietic lineage soon joined endothelial cells as recognized cellular components of the tumor microenvironment milieu. Angiogenic cytokines and their corresponding receptors were included in the party. The emerging concepts of angiogenesis versus vasculogenesis (3), vascular normalization (6), vessel co-option (7), vasculogenic mimicry (8), and metronomic chemotherapy (9) opened up the field to a new era of discovery, technological advances, and healthy debates.

The increasing acceptance of the role that the VEGF pathway plays in tumor angiogenesis eventually paved the way for a new class of anticancer drugs. One of the earliest proof of concepts of the potential of antiangiogenic drugs was a VEGF-specific mAb, which inhibited the growth of and vessel density in tumors, but had no effect on tumor cell growth rate in vitro (10). These observations eventually led to the clinical development and approval of the first antiangiogenic drug, bevacizumab, for metastatic colorectal cancer in 2004, 30 years after Dr. Folkman’s publication on tumor angiogenesis factor in Cancer Research. There have since been approvals of additional angiogenesis inhibitors: small-molecule tyrosine kinase inhibitors targeting VEGFR(s) (axitinib, cabozantinib, lenvatinib, pazopanib, regorafenib, sorafenib, sunitinib, vandetanib), protein therapies directed against VEGFR2 or VEGF/PIGF (ramucirumab and ziv-afibercept, respectively); and small-molecule mTOR inhibitors (everolimus and temsirolimus). Several other drugs known to possess antiangiogenic properties were approved to treat cancer although the precise mechanisms of action are not well understood. Thalidomide was one such drug; shelved due to birth defects in the 1950s and 1960s, it was repurposed to treat multiple myeloma after its antiangiogenic properties became known (11).

The genesis of antiangiogenic therapy was met with much enthusiasm and excitement, followed by press coverage, which at times became rather sensational. Rumors of a cure reached new heights, but Dr. Folkman quickly discounted such claims, stating “if you have cancer and you are a mouse, we can take good care of you” (12). This quote still rings true today. Antiangiogenesis therapy has had some successes but also its fair share of disappointment. The clinical benefit is typically modest, toxicity occurs, acquired resistance emerges, and the biomarker(s) that will predict which patients will respond to VEGF-targeted therapy remains elusive. However, despite these shortcomings, many of these antiangiogenics are routinely administered as standard of care in the clinic as they can extend survival times and/or delay disease progression.

On this 75th anniversary of Cancer Research, let’s reflect back on the pioneering work of Dr. Judah Folkman with gratitude for his outstanding scientific achievements, cherished mentorship, and tireless dedication to improving the lives of cancer patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
References

Commentary on Folkman: "Tumor Angiogenesis Factor"

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