Cutting the Supply Line

The story of Judah Folkman

By Dan Dou

Harvard researchers have contributed to numerous and significant biomedical breakthroughs over the university's 375-year history, but few of these discoveries can rival the relevance today at the level of Judah Folkman's crusade against tumor angiogenesis. Folkman set a paradigm and forged a new field in the face of skepticism from his scientific contemporaries.

With continuing advancement in the field of cancer research and development of novel therapies, cancer today remains a devastating diagnosis but is becoming more treatable in most cases.

Significant attention has paid to developing strategies to prevent and control metastasis, the spreading of cancer to other parts of the body. In many cases, an isolated localized tumor can be treated far more effectively than tumors that arise from cancer cells that travelled through the blood stream (1).

Present research targeting metastasis would not have been possible without the groundbreaking work of Judah Folkman in the 1960s and 1970s at Harvard. Folkman, referred to by many as the "Father of Angiogenesis" (2), founded an entire field of research devoted to understanding tumor angiogenesis, the critical process by which cancer tumors create a self-sustaining blood supply (3), and himself made great contributions toward this goal.

"Folkman, known by many as 'The Father of Angiogenesis,' founded an entire field of research."

The Founder of a Field

Born Moses Judah Folkman in Cleveland, Ohio in 1933, Folkman was the son of a rabbi but developed a strong interest in medicine at a young age through visiting hospital patients with his father. After his undergraduate studies at Ohio State University, Folkman attended Harvard Medical School, where he trained to become a surgeon. While at Harvard Medical School, Folkman exhibited great promise as a scientific researcher; he developed one of the first pacemakers before graduating in 1957 (4). The crucial research that would serve as the foundation for his legacy was yet on the horizon.

While completing his residency and serving as chief resident at Massachussetts General Hospital, Folkman became interested in researching tumor blood supplies through observing hundreds of juvenile cancer patients. At the time, angiogenesis and the general processes by which cancer tumors were nourished were very poorly understood. It was at this critical juncture in his career and development as a scientist that Folkman turned away from his previous research focus on mechanical devices, turning instead

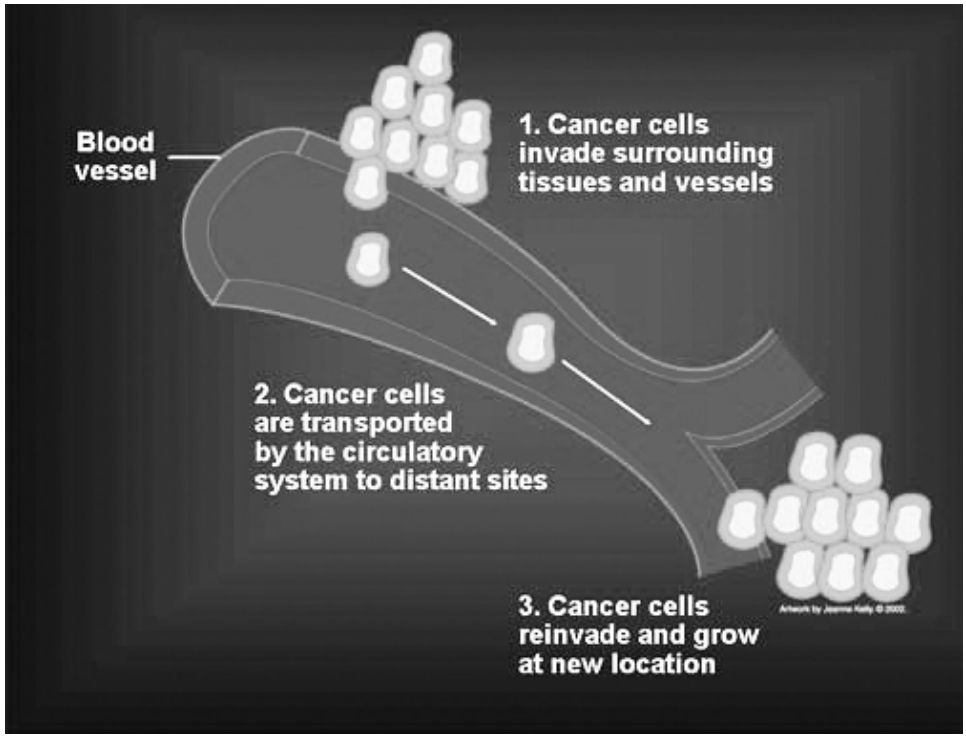

Figure 1. Metastasis, or the spread of cancer cells from one part of the body to another, occurs when tumor cells break off into a blood vessel, traveling through the bloodstream and forming a new tumor in another location.

toward understanding the biology of tumor angiogenesis.

What is tumor angiogenesis?

Tumors consist of a population of cancer cells containing mutations that inhibit the cells' ability to properly regulate their rate of growth and division. Cancer cells generally divide at a higher rate than do normal cells, thereby increasing the size of the tumor; however, the tumor cannot grow beyond a small size without forming extra blood vessels to deliver more oxygen and nutrients (3, 5). In order to induce blood vessel formation (angiogenesis), tumors secrete growth factors, such as vascular endothelial growth factor (VEGF) (3). New vessels grow in and around the tumor, providing connections between the tumor and the blood vessels leading to the rest of the body - the "host" circulation.

In cancer patients, tumor angiogenesis is a particularly significant issue because not only does blood vessel growth allow tumors to grow to larger sizes, but individual cancer cells or small clumps of the tumor can enter newly formed vessels and be away from the tumor into the host blood supply. These cancer cells can become lodged elsewhere in the body, such as in the lung or the brain, and develop into new tumors. The occurrence of metastasis can greatly worsen a patient's prognosis (1).

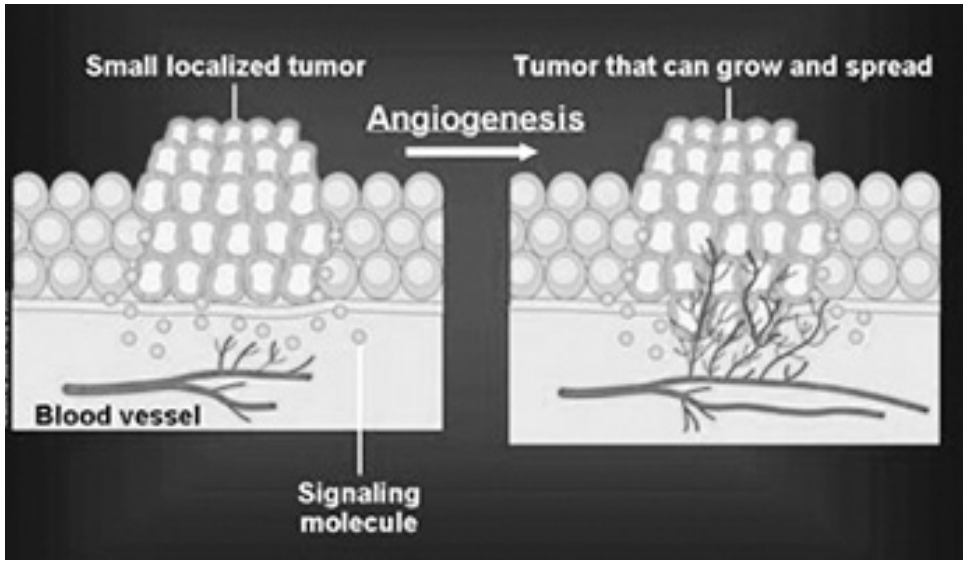

Figure 2. Tumors grow by creating a blood supply for themselves through the formation of tiny vessels called capillaries, in a process called tumor angiogenesis. Without these blood vessels, the tumor cannot exceed a small size.

Controlling the Blood Supply

When Folkman started his research on tumor angiogenesis, it was known that cancerous tumors were fed by tiny blood vessels called capillaries. However, it was Folkman who first suggested that tumor growth could be stopped by blocking this blood supply. Folkman conducted a study using mouse melanoma cells, with the goal of discovering the mechanism by which blood vessel-production is regulated in mammals and furthermore whether this information could be used to control cancer in other environments. He found that, when transplanted outside the mice, the mouse tumors all grew to roughly the same size, despite showing the capability to grow to larger sizes when transplanted intact back into the host. Folkman concluded that the growth had been limited by the lack of blood vessels that would allow oxygen and nutrients to penetrate the tissue and promote further growth (6).

Convinced that tumors required the formation of new blood vessels to continue growing beyond a certain size, Folkman continued his research in his own lab while also working as a surgeon at Children's Hospital Boston.

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He would later say that he found working as a physician easier than working as a scientific researcher, yet he excelled at both. He became the surgeon in chief of Children's Hospital Boston when he was only 34. He continued, however, to put significant time into his research, and by 1971 he published his first findings on tumor angiogenesis in a paper that many consider to mark the birth of a new field of research aimed at treating cancer through counteracting angiogenesis.

In the paper, "Tumor Angiogenesis: Therapeutic Implications", Folkman laid out his theory on the dependence of tumors on blood supply, and the beginnings of how preventing this process could be used to effectively treat cancer. It was already known that tumors were capable of recruiting blood vessels within and around themselves; Folkman's major contribution in this paper was to reveal for the first time the extreme extent to which tumors are dependent on blood vessels. Folkman put forth the idea that the growth of tumor cells and capillary endothelial cells were interdependent, and that the two cell types could regulate the activity of each other in the physiological environment (6).

Folkman also suggested that manipulating vascular (blood vessel) growth in and around the tumor could control tumor growth. He even postulated that this could be accomplished through using antibodies to immunize the host against Tumor-Angiogenesis Factor (TAF), a factor that stimulates rapid growth of capillaries (7). The most promising approaches today have involved Vascular Endothelial Growth Factor (VEGF) rather than TAF, yet Folkman's approach demonstrates remarkable foresight. Decades after his initial observation, antibody-based drugs such as Avastin were first used clinically to limit angiogenesis, just as Folkman predicted.

▲ **Figure 3.** Judah Folkman was a highly successful physician as well as a scientific researcher. He was surgeon in chief here at Children's Hospital Boston. He once said that he found working as a physician easier than being a researcher.

▶ **Figure 4.** Folkman in his lab.

Folkman's research showed that once the blood supply was taken away from the tumors, rendering them non-vascular, the tumors were reduced in size and became dormant. Folkman predicted that these non-vascular tumors would not be able to metastasize, preventing formation of new tumors elsewhere in the body. Often the growth of an individual tumor is minimal in comparison to growths arising from metastasis and the development of vascular tumors in other parts of the body, so inhibiting metastasis could be an effective way to improve patient prognosis (1, 8).

The Development of a New Field

Folkman's work was not appreciated by his contemporaries in the years following the 1971 publication. Most cancer researchers and physicians, skeptical of Folkman's hypothesis, continued to focus on trying to directly kill the cancer cells in the tumors. They failed to recognize the wisdom and simplicity of targeting the source, the "supply line." However, this controversy and skepticism further drove Folkman to continue to pursue this research in subsequent decades in order to better understand how to shut off the tumor supply line.

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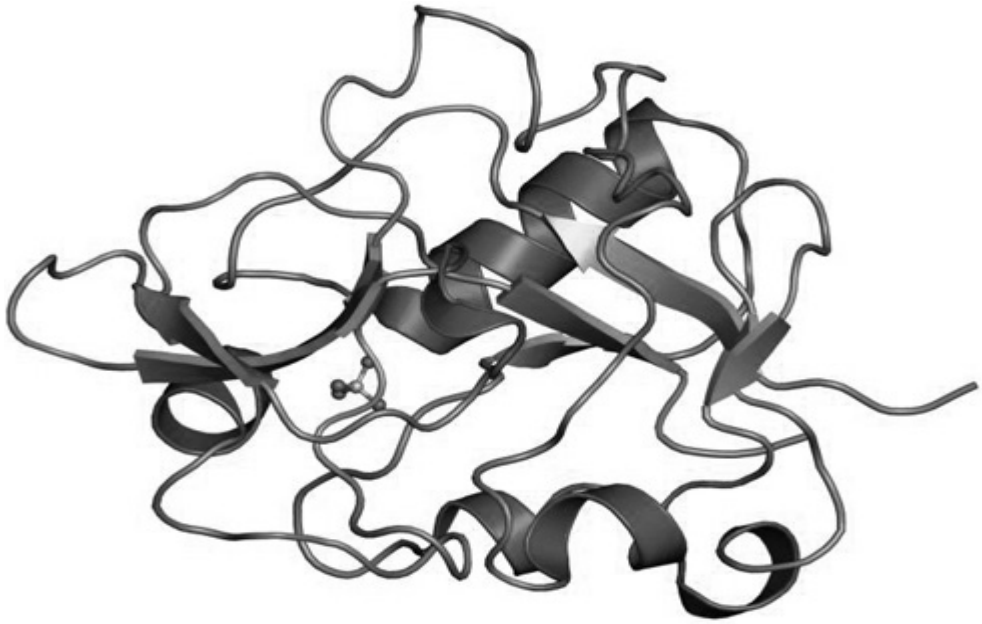
Folkman followed his earlier publication with the development of superior bioassays to improve analysis of angiogenesis and to allow for the collection of more concrete evidence on the relationship between and interdependence of tumors and their vasculature. However, the main goal of the remainder of Folkman's research career was to discover effective inhibitors of angiogenesis that could be used to treat patients. Folkman and his colleagues were the first to identify over a dozen examples of such inhibitors (2).



▲ **Figure 5.** Endostatin proved to be among the most potent inhibitors of angiogenesis that Folkman isolated. When the National Cancer institute successfully repeated Folkman's experiments with endostatin in 1999, the idea of anti-angiogenic therapy gained much credence.

Folkman's Legacy

Despite the initial indifference and resistance to Folkman's pioneering ideas following 1971, Folkman persevered with his research. In 1994, Folkman finally performed the experiment that brought nearly unambiguous support to his theories from the scientific community. Folkman showed that angiostatin, an angiogenesis inhibitor that he had isolated, could effectively stop lung cancer from growing in mice by inhibiting blood vessel formation (10). Afterwards, he obtained even stronger results with more potent inhibitors, including endostatin, avastin, and vasculostatin. The National Cancer Institute successfully repeated Folkman's endostatin experiments in 1999 (11), finally convincing many researchers and physicians that anti-angiogenic therapy was a viable cancer treatment to pursue clinically.

"Folkman put forth a new approach to cancer treatment that merited discussion, further research, and eventually clinical use."

Folkman's research is important because it sheds light on the mechanisms by which tumors are able to obtain oxygen and nutrients, and also on how these processes can be effectively inhibited. More significantly, Folkman put forth a new approach to cancer treatment that merited discussion, further research, and eventually clinical use (6, 12). Anti-angiogenic treatments are now commonly used in conjunction with other chemotherapeutic treatments at many cancer centers such as the Dana Farber Cancer Institute in Boston.

It is now widely understood how crucial tumor angiogenesis and its inhibition is to stopping and reversing tumor growth, and tumor angiogenesis today is one of the most popular fields in cancer research today.

Inhibition treatments targeting angiogenesis have already made the transition to clinical use, and are now used to improve the efficacy of other cancer treatments. As Folkman predicted in 1971, the ability to fully inhibit tumor angiogenesis may mean completely crippling the tumor's ability to grow and metastasize. Research today continues to better our growing understanding of tumor angiogenesis with the goal of developing strategies to completely sever the supply line as a front line therapeutic approach. H

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