What tumors need: a brief history of angiogenesis

The field of angiogenesis began in the early 1970s when Judah Folkman proposed that tumor growth would be halted if the tumor were deprived of a blood supply. Thirty years later, Folkman’s controversial idea is now widely accepted and angiogenesis inhibitors hold great promise for the treatment of cancer.

Dog thyroids and guinea pig eyes
Judah Folkman’s radical idea began with a mundane task. In 1961, Folkman, then a third year surgical resident, was drafted by the navy and charged with optimizing the use of freeze-dried hemoglobin as an alternative to fresh blood. The hemoglobin preparations were tested for the ability to sustain the viability of dog thyroid glands and, later, the growth of mouse tumor cells implanted in the glands. The implanted tumors stopped growing after reaching a modest size, but grew explosively if transplanted back into a mouse. Intrigued, Folkman examined the tumors under the microscope and found a network of tiny blood vessels inside the retransplanted tumor cells. He saw no vessels in the original thyroid tumors (1).

The data were consistent with work from Harry Greene, who had shown long before that growth of rabbit tumors transplanted into the anterior chamber of the guinea pig eye coincided with the growth of new blood vessels (angiogenesis). Tumors that remained viable but did not grow had no visible blood supply (2). Folkman thus proposed that angiogenesis and tumor growth might go hand in hand. He even stuck his neck out and speculated that “anti-angiogenesis” strategies might eventually be used to treat cancer (3). These ideas were widely criticized, as the prevailing opinion at that time was that tumor growth did not depend on angiogenesis.

Making the connection
Folkman and his student Michael Gimbrone took advantage of the eye transplant model to demonstrate that tumor fragments refused to grow if placed too far away from blood vessels. By contrast, tumor fragments implanted directly onto the iris—which has abundant blood vessels nearby—grew to 16,000 times their original size in only 2 weeks (4). Moving the distant, dormant tumors closer to the iris jump-started their growth. This suggested that tumor dormancy was caused not by cell cycle arrest or immune control, as most tumor biologists believed, but by a lack of blood supply.

But how did proximity to blood vessels dictate tumor growth? Previous studies had shown that tumor-stimulated vessel growth did not require direct contact between tumor and host tissue (5, 6), indicating that a soluble factor was at work. This made sense to Folkman, who reasoned that a soluble factor would be more likely to reach nearby than distant blood vessels. He and his colleagues later isolated a soluble tumor-derived factor that triggered endothelial cell proliferation and growth of capillaries in rat skin (7). They named the factor tumor angiogenesis factor (TAF). Both this and the eye transplant study were published in the Journal of Experimental Medicine.

Angiogenesis research explodes
With time and increasing evidence, the field was convinced of Folkman’s angiogenesis theory. “By the mid-1980s,” Folkman says, “we began to convert our critics into competitors.” And although the identity of TAF in his original preparation was never revealed, Folkman’s group and many others went on to discover numerous tumor-derived angiogenesis factors including basic fibroblast growth factor, angiogenin, and vascular endothelial growth factor (VEGF) (for review see reference 8). Later genetic studies in mice con-

FROM THE ARCHIVE

Judah Folkman in 2003. Courtesy of Children’s Hospital, Boston, MA.