The Search for Factor X: Clues from Cancer Biology

Angiogenesis is a normal developmental process, but in adults it is usually restricted to wound healing or to the female reproductive system. Outside of these physiological processes, angiogenesis is typically pathological, and occurs in many cancers and eye diseases.

In 1948, ophthalmologist I. C. Michaelson proposed that the eye secretes a growth factor that causes blood vessel growth and leakage in eye disease. However, this growth factor, coined “angiogenic factor” by Michaelson and later referred to as “Factor X” in ophthalmology, remained unidentified for nearly half a century.

Clues to the identity of Factor X came from the field of cancer research. Just as in eye disease, angiogenesis was known to occur in tumors, and in the late 1960s scientists hypothesized that tumors secrete substances that stimulate and attract new blood vessels. Judah Folkman, a medical scientist at Harvard Medical School and Boston Children's Hospital, realized that angiogenesis could fuel the growth of tumors and facilitate the spread of cancer. In 1971, Dr. Folkman published his seminal theory that angiogenesis inhibitors could be used to treat cancer and other angiogenesis-dependent diseases such as diabetic retinopathy. Although initially met with skepticism, this theory formed the basis of the field of tumor angiogenesis, as well as the award-winning research of the 2014 Champalimaud Vision Award Laureates in ophthalmology.

In 1989, working at the biotechnology giant Genentech, Dr. Ferrara isolated and characterized VEGF. The same molecule had been isolated a few years earlier as “vascular permeability factor” by Harvard Medical School’s Harold Dvorak and Donald Senger, who described its ability to make blood vessels leaky. However, Dr. Ferrara and colleagues additionally demonstrated VEGF’s potent angiogenic effects. VEGF quickly became a major research focus for anti-angiogenic cancer therapy.

Many angiogenic factors are produced by the body, and in the decades that followed Michaelson’s hypothesis, several candidates for Factor X were isolated. However, VEGF is unique among angiogenic factors because it not only stimulates blood vessel growth, but also causes vascular leakage, which is also a feature of various eye diseases (including neovascular AMD and diabetic retinopathy). Moreover, VEGF is stimulated by hypoxia (lack of oxygen), another condition known to induce angiogenesis in the retina. Thus, at Folkman’s suggestion, several researchers from Harvard Medical School explored VEGF as a potential Factor X in ocular disease.

Mutually Synergistic Research Spanning Academia and Industry

In the 1990s, the 2014 Champalimaud Award Laureates embarked on a series of scientific and clinical studies that were alternately collaborative and parallel—but always mutually interdependent and ultimately implicating VEGF in ocular disease.
Working with Dr. Folkman at Boston Children’s Hospital and Harvard Medical School, Drs. Adamis and D’Amore showed that retinal cells produce VEGF, and together with Dr. Ferrara, demonstrated its regulation by hypoxia. In a subsequent study, Dr. Aiello demonstrated in retinal cells that hypoxia stimulates VEGF, which in turn stimulates the proliferation of endothelial cells (the cell type that forms the lining of blood vessels).

Together with Dr. Miller of Mass. Eye and Ear, Drs. Adamis, D’Amore, and Folkman then associated VEGF with ocular angiogenesis in an experimental model of laser-induced retinal ischemia and ocular neovascularization. This was the first study to link VEGF with angiogenesis in a living organism.

In 1994, Dr. Adamis, Miller, and Folkman (working at Mass. Eye and Ear) published the first article describing increased VEGF in diabetic retinopathy. Shortly thereafter, Drs. Aiello, King, and Ferrara (in a larger study conducted between Joslin Diabetes Center and Genentech) found increased levels of VEGF in patients with angiogenic retinal disorders, including proliferative diabetic retinopathy.

The following year, Drs. Aiello, Ferrara, and King demonstrated that VEGF inhibition using soluble VEGF receptors could suppress oxygen-induced retinal neovascularization. Then, in 1996, Adamis, Gragoudas, Ferrara, Folkman, D’Amore, and Miller demonstrated suppression of laser-induced ocular neovascularization with anti-VEGF antibody, which was the precursor to bevacizumab (Avastin®).

At Genentech, Dr. Ferrara and colleagues performed experimental intraocular injections with full-length anti-VEGF antibodies and antibody fragments, and finding that the antibody fragments could rapidly penetrate the retina, they proceeded to test the anti-VEGF antibody fragment (Lucentis®) in patients with neovascular AMD.

At Mass. Eye and Ear, Drs. Adamis, Gragoudas, and Miller tested Genentech’s anti-VEGF antibody fragment in a preclinical model and showed that it safely prevented choroidal neovascularization—the type of blood vessel growth that occurs in wet AMD—and decreased the leakiness of existing choroidal neovascularization. This provided proof of principle to support the ongoing clinical trials of Lucentis®.

Drs. Gragoudas, Miller and Adamis also examined the ocular delivery of anti-VEGF RNA aptamers and oversaw clinical trials of the aptamer pegaptanib (Macugen®) for neovascular AMD, which would form the basis of FDA approval of Macugen® as the first anti-VEGF ophthalmic drug in 2004.

Then, in 2006, Lucentis® demonstrated remarkable results in phase III multicenter randomized controlled trial for neovascular AMD, leading to its regulatory approval for the treatment of neovascular AMD.

ADDITIONAL LINKS

National Eye Institute: Eye Health Information http://www.nei.nih.gov/health/

Nature Focus: Angiogenesis http://www.nature.com/focus/angiogenesis

NOVA ScienceNow Profile: Judah Folkman http://www.pbs.org/wgbh/nova/body/judah-folkman.html
World Health Organization: Priority Eye Diseases

About the 2014 Champalimaud Laureates

Besides co-discovering the role of VEGF in eye disease, the 2014 Champalimaud Laureates have made additional noteworthy biomedical contributions and currently oversee active research groups.

Concurrent with his collaborations with the 2014 Champalimaud Laureates, Dr. Ferrara developed monoclonal antibodies that suppressed the growth of a variety of cancers by preventing the growth of new blood vessels into solid tumors. These findings led to development of the anti-angiogenesis drug bevacizumab (Avastin®), which has become standard therapy for a variety of cancers. Dr. Ferrara has won many awards for his achievements, including the 2010 Lasker-DeBakey Clinical Medical Research Award, which frequently precedes the Nobel Prize.

Dr. Adamis co-founded Eyetech Pharmaceuticals in 2000, where he helped lead the development of pegaptanib (Macugen®) as the first anti-VEGF drug in ophthalmology. While at Eyetech, he also initiated the development of the first anti-PDGF-B drug in ophthalmology, a therapy that is used in conjunction with anti-VEGF therapy to further improve vision. The drug combination is currently in Phase III trials. After moving to Genentech/Roche, Dr. Adamis helped lead the team that obtained FDA approval for ranibizumab (Lucentis®) for diabetic macular edema and retinal vein occlusion.

Besides identifying VEGF’s role in eye disease, the Dr. Gragoudas and Dr. Miller are also credited with the development of photodynamic therapy with verteporfin (Visudyne®) from preclinical studies to clinical trials to agency approval for the treatment of neovascular AMD. A light-activated drug, Visudyne® destroys abnormal blood vessels under the retina and stops their leakage. As the first AMD treatment approved by the FDA (in 2000) and international drug regulatory agencies, Visudyne® opened the pharmacologic era of retinal disease therapy and was a first-line treatment for wet AMD before the advent of anti-VEGF therapy.

Dr. Gragoudas additionally pioneered the development of proton beam therapy for uveal melanoma, a potentially lethal cancer of the eye. He is Charles Edward Whitten Professor of Ophthalmology at Harvard Medical School and Director of the Retina Service at Mass. Eye and Ear.

Dr. Miller currently serves as Chair and Henry Willard Williams Professor of Ophthalmology at Harvard Medical School, and Chief of Ophthalmology at Mass. Eye and Ear and Massachusetts General Hospital. Dr. Gragoudas is the Charles Edward Whitten Professor of Ophthalmology at Harvard Medical School and Director of the Retina Service at Mass. Eye and Ear. They co-direct the Angiogenesis Laboratory at Mass. Eye and Ear and have both received numerous awards, including the Mildred Weisenfeld Award for Excellence in Ophthalmology, one of the highest individual distinctions awarded by the Association for Research in Vision and Ophthalmology (ARVO).

Dr. D’Amore is noted for her scientific contributions to the understanding of VEGF biology and angiogenesis. She isolated and characterized the murine VEGF gene and developed a widely used model...
of oxygen-induced retinopathy. Both systems have served as the cornerstone of numerous scientific studies and preclinical studies of therapies targeting angiogenesis, and the report describing the oxygen-induced retinopathy model is the most-cited article ever in the journal Investigative Ophthalmology and Visual Science. She is Professor of Pathology and Charles L. Schepens Professor of Ophthalmology at Harvard Medical School, and serves as Director of the Howe Laboratory at Mass. Eye and Ear and Director of Research at Schepens Eye Research Institute of Mass. Eye and Ear.

Dr. Aiello and Dr. King have made significant progress toward understanding, manipulating and inhibiting the expression, regulation, and signaling functions of VEGF and its receptors. In 1989 Dr. King proposed that activation of protein kinase C (PKC) is the major mechanism by which hyperglycemia disrupts the retina, kidney, and cardiovascular systems in diabetes. Drs. Aiello and King subsequently published the first evidence that PKC is involved in vascular leakage in diabetic retinopathy in part mediating the VEGF pathway. They went on to develop and evaluate an orally administered PKC-beta inhibitor for diabetic macular edema —thus opening a new therapeutic avenue for diabetic and other retinopathies.

Dr. Aiello helped found and then served as the inaugural chair of the Diabetic Retinopathy Clinical Research Network (DRCR.net), a national collaborative network funded by the National Eye Institute. The DRCR.net performed the first large randomized controlled clinical trial proving the benefit of VEGF inhibition for the treatment of diabetic macular edema. Dr. Aiello is Professor of Ophthalmology at Harvard Medical School, and at Joslin Diabetes Center, he serves as Vice President of Ophthalmology, Head of the Section on Eye Research, and Director of the Beetham Eye Institute.

Dr. King is Professor of Medicine at Harvard Medical School and at Joslin Diabetes Center he is Director of Research and Head of the Section on Vascular Cell Biology. He leads the Medalist Study, a comprehensive study to identify protective factors in a large group of type 1 diabetic patients with diabetes duration over 50 years. His numerous honors include the Cogan Award, one of the highest individual distinctions awarded by the ARVO.

About the Champalimaud Foundation

The Champalimaud Foundation, created in 2005 by the last will and testament of António de Sommer Champalimaud, focuses on cutting-edge research and strives to stimulate new discoveries and knowledge which can improve the health and well-being of people around the world. The Champalimaud Centre for the Unknown, based in Lisbon, Portugal, hosts the Foundation’s activities in the fields of Neuroscience and Oncology by means of research programmes and the provision of clinical care of excellence. The fight against blindness is also supported through a focused outreach programme. In seeking to achieve significant advances in biomedical science the Champalimaud Foundation has adopted a translational methodology, which establishes a direct link between research carried out in the laboratory and the diagnosis and treatment offered in the clinic. This connection and interdependency is at the core of the Foundation’s mission to bring the benefits of biomedical science to those most in need. More than anything, the Champalimaud Foundation works to improve the health and well-being
of humanity by actively searching for solutions which can alleviate the burden of disease in individuals and in society as a whole. On October 5th 2010 the Champalimaud Foundation inaugurated an innovative research facility to contribute to its objective of developing biomedical research activities in Portugal.

**Vision Award:** The Champalimaud Vision Award is given in alternate years for contributions to overall vision research (even numbered years) and contributions to the alleviation of visual problems, primarily in developing countries (odd numbered years). The recipients of the award are productive laboratories/organizations or collaborative efforts and this may involve groups from more than one institution or discipline. The Award does not focus only on the largest global organizations but on organizations of any size that can demonstrate high impact achievements. These could be on a local, national, regional or international level. The jury of the award consists of a distinguished panel of leading international scientists and of exceptional public figures involved in meeting the needs of the developing world. The award may be used in any way that furthers the outstanding contribution of the recipients. The António Champalimaud Vision Award has the support of Vision 2020 – The Right To Sight, a global initiative for the prevention of blindness launched in association with the World Health Organization and the International Agency for the Prevention of Blindness.

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