I spent my summer reading and thinking about trophoblasts. Trophoblastic cells form the layer of embryonic tissue that attaches the embryo or fetus to the wall of the mother's uterus. Trophoblasts provide protective armor by completely surrounding the embryo, while also carrying nutrients from the mother's blood to that of the developing fetus. The National Institutes of Health (NIH) define trophoblast as “the extra-embryonic tissue responsible for implantation, developing into the placenta, and controlling the exchange of oxygen and metabolites between mother and embryo.”

The word trophoblast means “original feeding tissue” and was so named by the Dutch embryologist Ambrosius Arnold Willem Hubrecht (1853-1915), who discovered it in the course of his study of the placenta of the hedgehog (Erinaceus europaeus). Soon trophoblasts were identified in other mammals, including man - or, rather, woman.

Most Western people are vaguely aware of the placenta, or afterbirth, which is the final act in the life drama of the trophoblast. In some cultures, the placenta is honored. According to one author, the Balinese wash the placenta in perfumed water after birth, wrap it in a cloth, and then bury it on the threshold of the family home in a carefully prepared coconut (Young 2001). The ancient Egyptians preserved the Pharaoh’s placenta in a special jar. The Japanese used to bury placentas in a cedarwood placental pot, and even today, the website of the Osaka City Bureau of Waste Management offers to dispose of an afterbirth for 1,700 Yen (about $14 USD). Perhaps our haste to dispose of afterbirth reveals some subliminal fear. One leading expert on placentas, the late Dame Anne McLaren, revealed in a scientific account that she had “always found trophoblast rather scary.”

Trophoblasts are unique in many ways, not least for their explosive growth rate. In the mouse, for example, between days 3 and 7 after conception, there is a 500-fold increase in tissue volume. This is mainly due to the power of the burgeoning trophoblast. What is more, “trophoblast is able to organize its own program of development within a well-defined time span that is independent of the embryo,” according to Y.W. Loke of King's College, Cambridge.

Although the placenta comes between the mother and the developing baby, it is independent of both. It arises before the embryo - the first differentiation of the fertilized egg is into trophoblast - and it has a separate life cycle. Having done its remarkable job, it dies upon delivery of the afterbirth, while the baby (hopefully) goes forward to a long and glorious life. Both scary and autonomous, and growing at an enormous rate, the placenta is rather like the Monster that Ate Pittsburgh.

In the early part of the twentieth century, scientists began to notice a remarkable similarity between trophoblastic cells and cancer. It was said that if you mixed up microscope slides of both trophoblasts and cancer, you could never again tell them apart. Both tumor tissue and trophoblast are highly proliferative, migratory, and invasive, with an almost limitless ability to perpetuate themselves unless checked.

The main difference between cancer and trophoblast is that trophoblast’s growth is a naturally self-contained process, limited to the environment of the uterus. In rare instances, however, trophoblast can escape from these natural boundaries, and the result is choriocarcinoma, a highly malignant form of cancer that is deadly, unless treated by chemotherapy. In the vast majority of cases, the cancer-like growth of trophoblast is kept in check by a cascade of hormonal and cytokine signals.

Over the past several years, there has been a stream of articles on the similarity between cancer and these trophoblastic cells of pregnancy. Here are excerpts from a few recent examples:

“The metastatic properties of cancer may also have its counterpart in the migratory behavior of germ cells, and in the propensity of normal trophoblast cells to migrate to other organs....” – L. Old, 2001
"Extravillous trophoblast cells are...reminiscent of cancer cells." – F. M. Corvinus et al., 2003

"Extravillous trophoblast cells resemble malignancies in their invasive and destructive features..." – T. G. Poehlmann et al., 2005

"Trophoblast cells have remarkable growth and invasive properties in vivo, so much so that they resemble neoplastic cells..." – Y.W. Loke in A. Moffett et al. 2006

In 2007, Dominique Bellet and her Parisian colleagues conducted a comprehensive review of the points of resemblance between trophoblast and cancer at the molecular level. They remarked on the "striking similarities between the proliferative, migratory, and invasive properties of placental cells and those of cancer cells" (Ferretti et al. 2007). The many similarities of cancer and trophoblast have profound implications for both our understanding of the natural history of cancer and for its treatment. I find it sad that, with a few notable exceptions, such as Dr. Lloyd J. Old of Memorial Sloan-Kettering Cancer Center, most authors in the field remain unaware of the work of John Beard, DSc. Beard was a British scientist who, 100 years ago, wrote a series of journal articles and a popular book on the similarity of trophoblast to cancer. Beard was convinced that cancer was in fact trophoblast, the outgrowth in every instance of an aberrant germ cell.

At one time, Beard was taken quite seriously. For example, the celebrated Sir William Osler lauded Beard’s work in embryology, and newspapers regarded his utterances in embryology to be authoritative and final. Beard advocated, as the practical corollary of his theory, the use of intravenous pancreatic enzymes in cancer treatment. A great many physicians began using Beard’s treatment. However, Beard’s therapeutic hypothesis was eventually abandoned, possibly because of the fact that the various enzyme preparations available in those days were uneven in quality and easily destroyed by mishandling, and thus produced extremely inconsistent results. Today, Beard doesn’t even merit an entry in Wikipedia. Given the growing interest in the similarity of cancer and trophoblast, this might be an opportune moment for scientists to take a fresh look at John Beard’s thinking on this still largely unexplored subject.

Doubts about Angiogenesis Inhibitors

New doubts have been raised about the safety and efficacy of drugs known as angiogenesis inhibitors. These drugs are designed to block the development of new blood vessels within and around tumors. Without an effective and independent blood supply, a tumor cannot grow bigger than the tip of a pencil.

This strategy for combating cancer was first put forward in the early 1970s by Judah Folkman, MD, of Harvard Medical School (Folkman 1971). Folkman believed that drugs based on his research would not only be more effective but far safer than traditional cytotoxic chemotherapy. After an initial period of intense resistance the idea caught on big time. There are now thousands of articles on angiogenesis and cancer, hundreds of them by Folkman himself. More importantly, many of the newly approved cancer drugs are based on this concept of attacking the tumor’s blood supply. But while the theory itself is elegant, and Folkman has become an icon of modern medicine, there are serious questions about how safe and effective many of the current generation of anti-angiogenic drugs are in controlling tumor growth.

A study from the University of California at Los Angeles (UCLA), published in August, 2007 in the peer-reviewed journal Cell, shows that a widely used group of anti-angiogenesis drugs is associated with serious and potentially deadly side effects. These drugs are known as VEGF inhibitors. (VEGF stands for vascular endothelial growth factor, a signaling protein that promotes the growth of new blood vessels.)

Outside-In Vs. Inside-Out

Many of the currently used VEGF inhibitors such as Avastin (bevacuzimab) work by blocking VEGF signaling from outside the cell. However, the UCLA researchers are trying to understand what happens when VEGF signaling is blocked from within the cell, which is a mechanism used by

---

Sytrinol™

"Healthy Cholesterol Levels... Naturally"

**Benefits:**
- Lowers Total Cholesterol
- Lowers Triglyceride Levels
- Lowers LDL Cholesterol Level
- Lowers LDL to HDL Cholesterol Ratio
- Elevates beneficial HDL

**150 Mg., 60 Soft Gel**

1-800-524-3727

Royal Nutrition International • Anaheim, CA 92807

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.*

---

TOWNSEND LETTER – DECEMBER 2007
some of the newer, small molecule anti-angiogenic drugs that are currently in late-phase clinical trials. According to a UCLA press release, “the result was unexpected and sobering.” More than half of the mice in the study suffered heart attacks and fatal strokes. The mice that remained alive developed serious systemic vascular disease, according to Luisa Iruela-Arispe, a professor of molecular, cell, and developmental biology and director of the Cancer Cell Biology program at UCLA’s Jonsson Cancer Center (Lee 2007).

“This was an extremely surprising result,” said Iruela-Arispe, past president of the North American Vascular Biology Organization and a national expert on angiogenesis. “I think this study is cause for some caution in the use of angiogenesis inhibitors in patients for very long periods of time and in particular for use of those inhibitors that block VEGF signaling from inside the cell.”

It is already known that five percent of patients taking Avastin develop blood clot-related side effects. Yet because Avastin was approved only three years ago, it is unclear what adverse effects may occur when patients remain on the drug for many years, according to Iruela-Arispe. In her three-year study, Iruela-Arispe created mice that were missing VEGF in the endothelial cells that line the inside of blood vessels and form the interface between circulating blood and the vessel wall. The UCLA team did not expect to see much of an effect because the amount of VEGF that is created inside endothelial cells is tiny compared to the amount created outside the same cells. But they soon had a bombshell finding: 55% of the mice died by 25 weeks of age, which is the equivalent of age 30 in humans. The remaining mice lived on, but were all very ill for the remainder of their lives.

“Some side effects have already been identified in people taking angiogenesis inhibitors,” said Iruela-Arispe. “And they’ve been along the lines of what we’re seeing in the lab.” Oddly, even high levels of VEGF outside the cells did not compensate for the absence of very tiny amounts within the cells. The missing internal VEGF had “a tremendous biological significance,” Iruela-Arispe said. “Clearly there is signaling from inside the cell that is different from signaling initiated outside the cell,” she added. “When there is no VEGF signaling inside the cell, the endothelial cells die. The intracellular part of the VEGF signaling loop is required for cell survival. This is the first demonstration that intracellular signaling is an important event.”

One of the most pressing concerns surrounding current angiogenesis inhibitors is the fact that they are associated with an increased risk of thrombosis (blood clots). Why does this happen? UCLA Prof. Luisa Iruela-Arispe’s study in the August 24, 2007 issue of Cell throws light on this urgent question. “I believe the survival function of VEGF signaling is mediated from both outside and inside the cell. When we block it from the inside, the outside signaling cannot compensate. But when we block it from the outside, maybe the inside signaling can compensate. That would explain the lesser side effects found when using drugs such as Avastin, which block the extracellular signaling.”

This aspect of angiogenesis inhibitors troubles Iruela-Arispe. Avastin, like most angiogenesis inhibitors, is generally infused systemically (i.e., given via a vein directly into the bloodstream). But Iruela-Arispe, who continues to believe in the therapeutic potential of angiogenesis inhibitors, thinks they could be made safer and more effective if they were delivered in a more tumor-focused way. “There is enough smoke in the sky here to make me feel there may be a fire,” she added, ominously.

Personally, I share her concerns. I have frequently expressed skepticism about many of the best-publicized “targeted” drugs. My reluctance to jump on the targeted therapy bandwagon has been based on my reading of the medical literature. Simply put, the current approach, at least with the present generation of anti-angiogenic drugs, is not particularly effective. As to toxicity, while these drugs were initially promoted as non-toxic magic bullets, there is now accumulating evidence of toxicity and sometimes lethal side effects. The interested reader can find dozens of my articles on targeted therapies by searching for terms such as Avastin, Erbitux, and Iressa at my website, www.cancerdecisions.com. The phrase “targeted therapy,” applied to these angiogenesis inhibitors, certainly has a nice ring to it. But the fact that these drugs can cause so many devastating adverse effects yet still be called “targeted” represents a triumph of public relations over science.

References