



The Weaker Vessel

**Evan David Rosen, M.D., Ph.D. Assistant Professor of Medicine,
Harvard Medical School**

One of the hottest ideas to hit the cancer world in the last decade is anti-angiogenesis therapy. Angiogenesis is the process by which new blood vessels are formed. Tumors can't keep growing unless their blood supply keeps pace, so blocking angiogenesis is a logical way to fight cancer. At least it seemed that way to Judah Folkman, a researcher at Harvard Medical School, who has achieved iconic status for his contributions in this area. There are now several anti-angiogenic agents in clinical trials for different cancers, and fortunes are being made and lost in the biotech battles to develop ever more potent drugs.

So what does this have to do with obesity and diabetes? Plenty, it turns out. One of the interesting attributes of fat is that it is the only normal tissue that can dramatically increase its mass during adult life. Think about it—you'd be hard pressed to increase the size of your liver, your lungs, or, sadly, your brain. But large numbers of Americans are having no trouble expanding their waists. In this way fat is reminiscent of tumor tissue, and like tumor cells, fat cells would get into trouble quickly if they didn't increase their blood supply as they grew.

This sort of thinking led scientists in Folkman's lab to try treating obese mice with different anti-angiogenic drugs originally developed for the fight against cancer. The results were actually quite impressive; these agents led to significant amounts of weight loss in all the different models of obesity tested. This slimming effect was associated with reduced food intake as well as increased energy burning, although the reasons behind these changes were not clear. The mice appeared healthy, and it's important to mention that they didn't lose all their adipose tissue. This is critical because the complete absence of fat, a condition called lipodystrophy, leads to even more serious health problems than obesity.

One important caveat is that the drugs used in the Folkman study were general blockers of angiogenesis. That means that they reduced blood vessel growth throughout the body, not only in fat. While the most obvious explanation for the weight loss was reduction of angiogenesis in the fat tissue, other explanations were also technically possible. Furthermore, you wouldn't really want to fight obesity with a drug that affects many different tissues at once.

A new study just published in the journal *Nature Medicine* puts this issue to rest. In this study, performed by a group at Baylor University in Texas, the blood vessels of adipose tissue were specifically targeted for inhibition. This was made possible by the discovery of a protein sequence that binds to the blood vessels of adipose tissue, and nowhere else in the body. By attaching this protein sequence to another protein that causes cell death, the investigators could target and destroy developing blood vessels in fat specifically. Consistent with the earlier data from the Folkman lab, this treatment resulted in significant weight loss in obese mice.

The Texas group went a step farther, however, by identifying the protein in the blood vessels of adipose tissue that allowed the specific targeting. It turns out that this protein, called prohibitin, is known to reside within all cells in the body, where it serves a variety of poorly understood functions. Despite its presence inside every cell, it seems (this was not explicitly proven, mind you) that prohibitin must hang out on the surface of the blood vessels in fat tissue, where it would be available for binding.

Lots of important questions remain about the basic biology of the system, but if these results are confirmed, it would give people a big bulls-eye to shoot for in the war on obesity. Given where we are in that battle, and where we need to be, any new targets are welcome.

Viewpoint is an editorial column that expresses the opinion of the specific Medical Director, who is solely responsible for its content. Viewpoint does not represent the views or opinions of Veritas Medicine and does not reflect the opinions of other physicians and researchers.

References

Maria A. Rupnick, Dipak Panigrahy, Chen-Yu Zhang, Susan M. Dallabrida, Bradford B. Lowell, Robert Langer, and M. Judah Folkman. From the Cover: Adipose tissue mass can be regulated through the vasculature. *Proceedings of the National Academy of Sciences* 2002 99: 10730-10735.

Mikhail G Kolonin, Pradip K Saha, Lawrence Chan, Renata Pasqualini, Wadih Arap. Reversal of obesity by targeted ablation of adipose tissue. *Nature Medicine* 10, 625 - 632 (01 Jun 2004).

Written by Evan D. Rosen, M.D., Ph.D.

Content created 6/10/04

This information was last reviewed June 10, 2004.