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Previews

# Treating Obesity Like a Tumor

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**Expanding adipose tissue in obesity requires a great deal of angiogenesis to support increasing volumes of tissue. A growing body of evidence indicates that inhibiting these blood vessels can result in substantial weight loss, and now this has been demonstrated in nonhuman primates.**

Extremely skeptical. That is the best description of my response to publications indicating that either diet-induced or genetic forms of obesity could be reversed by giving inhibitors to blood vessel formation. The first of these reports came from Maria Rupnick and Judah Folkman, who used agents that inhibit tumor growth and found profound weight loss in mice (Rupnick et al., 2002). The next of these reports used a more sophisticated approach in an attempt to direct the inhibition of the blood vessels specifically to adipose tissue. In an effort led by Wadih Arap and Renata Pasqulini, they used a technology called phage display that had been designed to identify the signatures of tumor-associated blood vessels that might be different than other blood vessels. However, they determined that many tissues, including adipose tissue, had unique properties. They were able to identify short peptide sequences that would selectively bind to the vasculature of white adipose tissue, but not other tissues they examined. As cancer researchers, they took the next logical step. They used this peptide and attached a poison pill that would produce apoptosis in the targeted blood vessels (Kolonin et al., 2004). This targeted approach also led to rapid and substantial weight loss in mice. In their most recent manuscript published in *Science Translational Medicine*, this group has extended these results to obese nonhuman primates, showing substantial weight and body fat loss after 28 days of treatment with this peptide (Barnhart et al., 2011).

The reason for my skepticism toward this approach centered on the assumption that, whether untargeted or targeted, reducing adipose tissue blood vessels would impair adipose tissue function. While obesity is a scourge to be fought and is the direct result of expanding adipose tissue, the truth is that healthy adipose tissue serves an important function to protect the rest of the body from nutrients that, when stored in other tissues such as muscle and liver, cause metabolic dysfunction. The most obvious example of this comes from humans or mice who fail to make sufficient adipocytes. While leaner, such individuals nevertheless have severe metabolic problems, including liver steatosis, hyperlipidemia, and severe insulin resistance (Huang-Doran and Savage, 2011). Thus, it seemed likely that such an approach that compromised adipose tissue function could result in leaner individuals who were more at risk for metabolic disease.

Ultimately, the data in mice and nonhuman primates simply do not support my assumption. In nonhuman primates, weight loss is accompanied by reduced insulin resistance (Barnhart et al., 2011). In mice, our own work has demonstrated that treatment with this peptide results in rapid weight loss that is primarily due to reduced intake, and it is accompanied by metabolic improvements (Kim et al., 2010). The important point here is that the response to targeting the adipose tissue vasculature is the exact opposite of what is observed when adipocytes are not present or are pushed into apoptosis. While removal of adipocytes is associated with increased intake and decreased insulin sensitivity (Pajvani et al., 2005), removal of the supporting vasculature results in decreased intake and increased insulin sensitivity (Kim et al., 2010). The conclusion to be drawn is that adipocytes are an important source of signals to both the brain and other tissues and that the removal of those signals is deleterious. Targeting the adipose tissue vasculature results in changes in adipocyte communication that promote weight loss and improved metabolic regulation.

This work has opened up an entirely unappreciated aspect of adipose tissue biology that explores the intimate relationship between adipocytes and their supporting vasculature. More importantly, understanding and manipulating this relationship has important therapeutic implications, given the potent effects of this particular peptide. A crucial question is whether this approach borrowed from cancer treatment is going to be sufficiently safe to be used in the growing number of individuals suffering under the burden of obesity and its comorbid conditions. After all, treating cancer is considerably different from treating a chronic condition such as obesity. Cancer patients are often under a short-term threat, while obesity is a much longer-term threat to an individual's health. As a consequence, the risk-benefit analysis is considerably different. For example, the specificity of the targeting is less of a concern in cancer as compared to obesity treatment. Imagine a peptide with 90% targeting selectivity to the tumor. Given that the plan would be to treat the cancer patient for weeks or months, as long as the tumor is being undermined faster than normal tissue, and that normal tissue can recover once treatment is terminated, it can be a viable therapy. For the obese patient who is likely to be taking such a treatment for the better part of his or her life, would 90% targeting selectivity be sufficient to avoid adverse effects on other tissues? Ninety-five percent? Ninety-nine percent? This is a complex question that will need to be answered before we know whether this approach will become therapy.

The important new insights driven by the work with these targeted peptides are an important advance in an

environment where few effective treatment strategies short of bariatric surgery are available to help obese patients. It is clear that more creative strategies from a wider range of disciplines are needed. To that end, further understanding of how adipose tissue signaling is altered by various aspects of its milieu, including the supporting blood vessels, macrophages, and its extracellular matrix, is necessary if we are to bring more therapies to the large unmet medical need presented by increasing rates of obesity.

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# Reactive Oxygen Species Resulting from Mitochondrial Mutation Diminishes Stem and Progenitor Cell Function

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**While age-dependent stem cell decline is widely recognized as being a key component of organismal aging, the underlying mechanisms remain elusive. In this issue of *Cell Metabolism*, Suomalainen and colleagues provide evidence that mitochondrial mutation and associated reactive oxygen species can adversely impact tissue-specific stem and progenitor cell function.**

Physiological aging invariably leads to a loss in normal tissue maintenance and reduced regenerative potential. The fact that these processes are normally under the functional purview of adult tissue-specific stem cells implicates age-associated stem cell decline as a fundamental contributor to the aging of tissues and organisms. Indeed, the importance of the stem cell compartment in contributing to age-associated pathophysiology has been demonstrated in a number of studies (Rossi et al., 2008). Consistent with the inherent complexity of physiological aging, the mechanistic basis for age-related stem cell decline is similarly complex, with evidence suggesting the involvement of cellular, genetic, and epigenetic components (Rossi et al., 2008). However, recent evidence from a number of papers, including a paper by Suomalainen and colleagues in this issue of *Cell Metabolism*, suggests that accumulating mitochondrial DNA damage may also be an important contributor to somatic stem cell decline with age.

Mitochondria are frequently referred to as the cell's "power plants" since they play a fundamental role in the production of adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS). Most aerobic organisms use some form of OXPHOS because it is a highly efficient method for producing ATP; however, the downside of this energy-producing pathway is that it also leads to the production of reactive oxygen species (ROS) that have the potential to damage cellular macromolecules and, in such a way, contribute to aging. Mitochondrial DNA (mtDNA) is believed to be highly susceptible to oxidative damage in part because of its proximity to the electron transport chain, but also because mtDNA lacks protective histones. Accumulation of damage in the mitochondrial genome has been proposed to lead to mitochondrial dysfunction and concomitant cellular decline and, in such a way, contribute to physiological aging (Harman, 1972). This long-held theory was supported experimentally with the generation of mtDNA "mutator" mice bearing a proofreading-deficient mtDNA polymerase (POLG) that exhibit a spectrum of degenerative phenotypes reminiscent of aging (Kujoth et al., 2005; Trifunovic et al., 2004). More recently, these mice have also provided the necessary experimental tool to address how mtDNA mutation accumulation impacts stem cell function and to determine whether it contributes to age-associated stem cell decline.

Within mammalian tissues, aging has been most comprehensively studied in