

# INTERVIEW about

## Fat Apoptosis Through Targeted Activation of Caspase 8 (FAT-ATTAC)

with

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### Why make a fatless mouse?

Utpal Pajvani: Adipocytes have been a historically understudied cell type, mostly because these modest cells were considered inert storage bags for excess lipid. These misconceptions have been systematically repudiated, and an expanding literature currently focuses on other parameters of adipocyte function, most notably the cadre of unique secreted products produced by adipocytes, collectively known as adipokines (including leptin, adiponectin and resistin). In addition, the opposing human conditions of obesity and lipodystrophy have strong, shared predilections for insulin resistance, diabetes and the metabolic syndrome, underscoring the intricate balance of adipose mass and function necessary to promote systemic well-being.

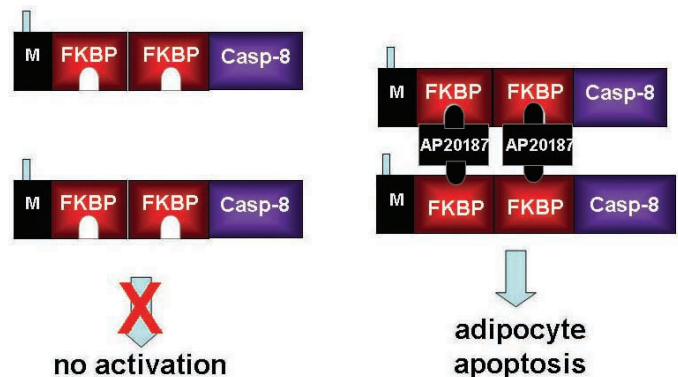
Transgenic mice that lack adipose tissue were engineered to more fully understand the complex roles of adipocytes, as well as provide

a mouse model for congenital lipodystrophies. The first described fatless mouse was derived by adipocyte-specific expression of an attenuated diphtheria toxin A chain which produced transgenic animals that showed a complete resistance to chemically induced obesity (1). A second effort produced by over-expression of the nuclear form of sterol regulatory element-binding protein-1c (nSREBP-1c) in an adipocyte-specific manner resulted in disordered differentiation of adipose tissue with marked reduction in systemic white adipose and resultant compensatory hypertrophy and morphological changes in brown adipose tissue (2). These mice, although lean, developed marked insulin resistance and a hyperglycemic phenotype. This phenotype is mirrored by a third, more completely characterized transgenic mouse model, named A-ZIP/F-1 which express, selectively in adipose tissue, a dominant negative protein that heterodimerizes with and inacti-

ates members of the C/EBP and JUN families of B-ZIP transcription factors with resultant inhibition of adipocyte differentiation. These mouse models collectively demonstrated a few fundamental principles: (a) adipocyte number and function can be genetically manipulated; (b) the complete absence of adipocytes, in parallel with the more fully

elucidated state of excessive adipocyte mass, produces a state of metabolic disarray consistent with several aspects of the metabolic syndrome described in humans (hyperlipidemia and insulin resistance); (c) the absence of functional adipocytes leads to a more widespread systemic effect marked by dysfunction of multiple organ systems (i.e. fatty liver).

Figure 2 - AP20187-mediated adipocyte apoptosis



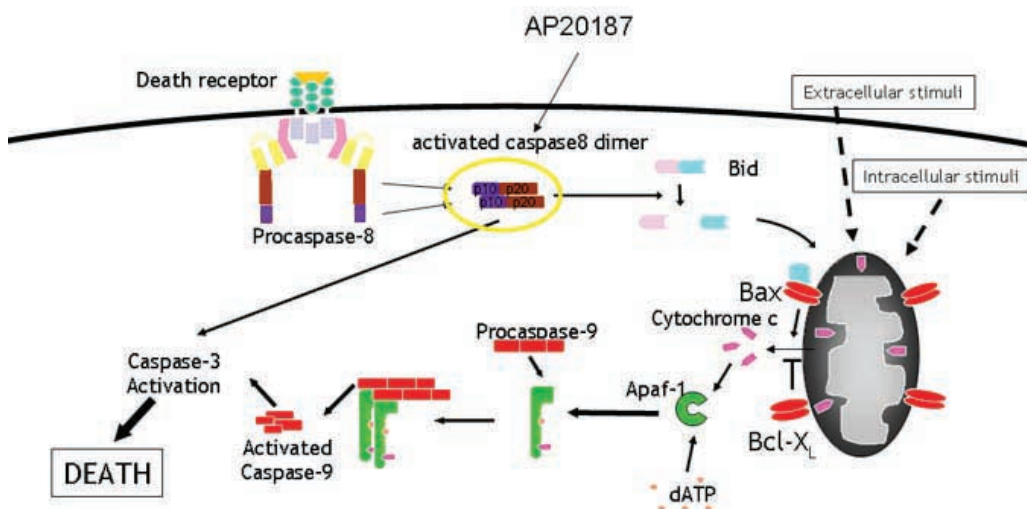
### What is the FAT-ATTAC mouse?

Utpal Pajvani: The FAT-ATTAC (*FAT* Apoptosis Through Targeted Activation of Caspase8) was created in order to produce the first inducible and reversible model of lipodystrophy (4). Briefly, we transgenically expressed a myristoylated caspase 8-FKBP fusion protein in adipocytes. Intraperitoneal administration of a chemical dimerizer (AP20187, a FK506 analog) effectively forces dimerization of membrane-associated caspase 8 through the FKBP domains (Figure 1,2). Activation of downstream

signaling cascades results in a specific apoptosis of adipocytes and ablation of functional adipose tissue at any stage in development and within 2 weeks of initiation of dimerizer treatment.

We wanted to produce a model system similar to the ones previously characterized in terms of absence of adipocytes, but desired greater control on the manipulability of the system. Previous models suffered from two fundamental limitations – there was no way to direct ablation of adipocytes in a temporally limited manner, nor was there any mechanism to “regrow” lost adipocyte mass. Both aspects are potentially critical for future study. The inducibility of adipose ablation in the FAT-ATTAC mouse avoids the secondary developmental complications of congenital lipodystrophy observed in other fatless mouse models – since we can induce apoptosis of adipocytes at any stage in development, we can study the metabolic profile of a mouse model in the absence of adipocytes prior to the pro-

Figure 1 - Cellular apoptosis pathways



gressive metabolic dysfunction that inevitably ensues. Furthermore, by allowing development in the presence of adipocyte function, we can ensure normal morphogenesis of various organ systems (i.e. mammary gland) prior to ablation, critical for determining the effects of “fat-

lessness” on development of breast cancer. In addition, the reversibility of adipose tissue ablation facilitates the study of many physiological and pathological processes – for instance, the process by which adipogenesis is critically dependent on angiogenesis (reviewed in 5).

### What role will the FAT-ATTAC mouse play in human disease?

**Utpal Pajvani:** Among the many possible avenues of study in both physiology and pathology that this mouse could be useful for, I envision the FAT-ATTAC mouse to provide an exquisitely sensitive model system for the discovery, design and testing of novel anti-obesity compounds – there has never been a cleaner, *in vivo* palate for the application of potential pharmaceuticals. Following induction of global adipocyte apoptosis, ensuring minimal (if any) residual functional adipocytes using the AP20187-based dimerizer system, the dimerizer is withdrawn allowing adipocyte regrowth – at this

stage, anti-obesity compounds could be systematically tested to determine which have the capability of preventing adipocyte regeneration from adipose-lineage specific stem cells yet to be identified. This regrowth can be non-invasively monitored by body weight, MRI or by the presence of circulating adipokines and finally confirmed by histological analysis of residual adipose depots. Potential therapeutic compounds that survive this relatively simple, yet novel, screen would then have to be tested in clinical trials in humans, having already proven efficacious in an *in vivo* system.

### REFERENCES

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