# New drugs from fat bugs?



**Signal transduction cascades, such as Hedgehog (Hh) signaling, are potentially important targets for new drugs. A new study in this issue of *Cell Metabolism* (Suh et al., 2006) identifies hedgehog signaling in the formation of the *Drosophila* fly body and in mammalian adipogenesis.**

The desire to control human adiposity has spurred a proliferation of studies on adipogenesis, and new pathways are continually being added to our map of this process. Much of what we know has come from studies in established pre-adipocytic cell lines such as 3T3-L1 and 3T3-F442A, which can be induced to differentiate by exposing them to pro-adipogenic cocktails including combinations of insulin, cAMP, glucocorticoids, and thyroid hormone. Other progenitor cell types such as ES cells, embryonic fibroblasts, and multipotent mesenchymal cell lines like C3H10t1/2 have also been used. Since the ultimate goal is to understand fat cell formation in vivo, it is fortunate that many, if not most, of the key findings derived from cell culture-based studies have held up reasonably well in transgenic and knockout mouse models. Because mice are not always easy to work with, and have their own limitations, a number of groups have turned to invertebrate systems, such as *C. elegans* and *Drosophila*, as models of adipogenesis. A new report from Suh et al. (2006) identifies the hedgehog pathway in fly fat body formation and goes on to show a similar role in mammalian adipogenesis. Moreover, they show that Hh signals appear to divert progenitor cells away from fat and toward bone formation.

Are flies and worms suitable models for mammalian fat cell biology? The answer is ''maybe,'' or perhaps more accurately, ''it depends.'' Certainly these animals have cells that can store calories as esterified lipid and then release them as fatty acids, a primary function of fat cells. Much of the enzymatic machinery that makes this possible is conserved through evolution, and biochemical and expression studies of these genes and proteins in lower organisms would seem to be fair game. Adipogenesis per se is a little trickier, in that there is debate over whether these lipid-storing cells can be considered truly orthologous to vertebrate adipocytes. In *Drosophila*, for example, the fat body is also the site of detoxification and sugar biosynthesis, a feature more reminiscent of hepatocytes. Cells of the fat body also participate in the immune system of the fly. In the end, however, the only thing that really matters is whether findings from these models can be shown to be relevant in more traditional systems. Despite the conservation of many developmental pathways, this hasn't been easy to accomplish. For example, serpent (*srp*) is one of three GATA-like factors in *Drosophila* and has been shown to play an important role in promoting fat body development in flies (Hayes et al., 2001). In mammalian systems, GATA factors are also involved in adipogenesis, but they are *anti*adipogenic (Tong et al., 2000, 2005). Thus, one's opinion of the utility of the invertebrate model of adipogenesis depends upon whether you think that the identification of GATA as a player in this process represents an important advance, or whether you believe that the opposite actions of GATA in mice and flies calls the whole enterprise into question. Similarly, Wnt signaling in mammals has strong antiadipogenic actions (Ross et al., 2000), while the actions of the orthologous wingless (*wg*) gene in flies are antiadipogenic in the dorsolateral fat body but proadipogenic in the ventral fat body (Riechmann et al., 1998).

Hedgehog signaling is another highly conserved pathway (Figure 1). In flies, hedgehog has profound effects on embryonic patterning, a role generally conserved in vertebrates. In mammals there are three hedgehog orthologs, including sonic hedgehog (Shh), Indian hedgehog (Ihh), and Desert hedgehog (Dhh). These secreted molecules have important developmental effects on multiple cell types, and various labs have attempted to look at the effect of hedgehog signaling on fat cell differentiation. Treatment of C3H10t1/2 cells with BMP-2 can promote osteogenesis and adipogenesis, and two groups have shown that Shh blocks adipogenesis in these cells while enhancing the osteogenic response to BMP-2 (Spinella-Jaegle et al., 2001; Zehentner et al., 2000). The suggestion was thus made that Shh might have something to do with mammalian adipogenesis, but the idea was not pursued further.

Into the breach comes the paper by Suh et al. in this issue of *Cell Metabolism*. These authors, strong proponents of invertebrate modeling of mammalian adipocyte biology, pulled the hedgehog receptor smoothened (smo) out of an enhancer trap experiment designed to find elements driving *Drosophila* fat body gene expression. Further analysis in the fly showed that activating the hedgehog pathway in a variety of ways (by overexpressing either Hh itself, its receptor Smo, or its downstream transcriptional effector, Ci) reduced lipid accumulation and tissue-specific gene expression in the fat body, and that a dominant negative Ci had the opposite effects. They next turned to mammalian fat cells and showed that components of the hedgehog signaling system are expressed in 3T3-L1 cells, with a pattern suggesting that expression of pro-hedgehog molecules declines during adipogenesis while molecules predicted to oppose hedgehog action rise. Direct exposure of Shh to 3T3-L1 cells inhibited adipogenesis, as did retroviral introduction of an activated form of the Shh receptor. Conversely, inhibition of hedgehog signaling by pharmacological blockade or by addition of a dominant-negative Gli (the mammalian ortholog of Ci) enhanced fat cell development. In C3H10t1/2 cells, Shh pushed cells toward an osteogenic fate at the expense of adipogenesis, as shown previously. Hedgehog signaling has several distal effectors, and the authors identified GATA as a mediator of the Shh effect on adipogenesis. This finding is particularly gratifying in that it connects the hedgehog story to a factor already known to be antiadipogenic.

There are several features that make this paper interesting. First, it identifies hedgehog as a player in adipogenesis from an unbiased screen, suggesting the general importance of the pathway. Second, it shows that hedgehog behaves similarly upon the biology of fatty tissues

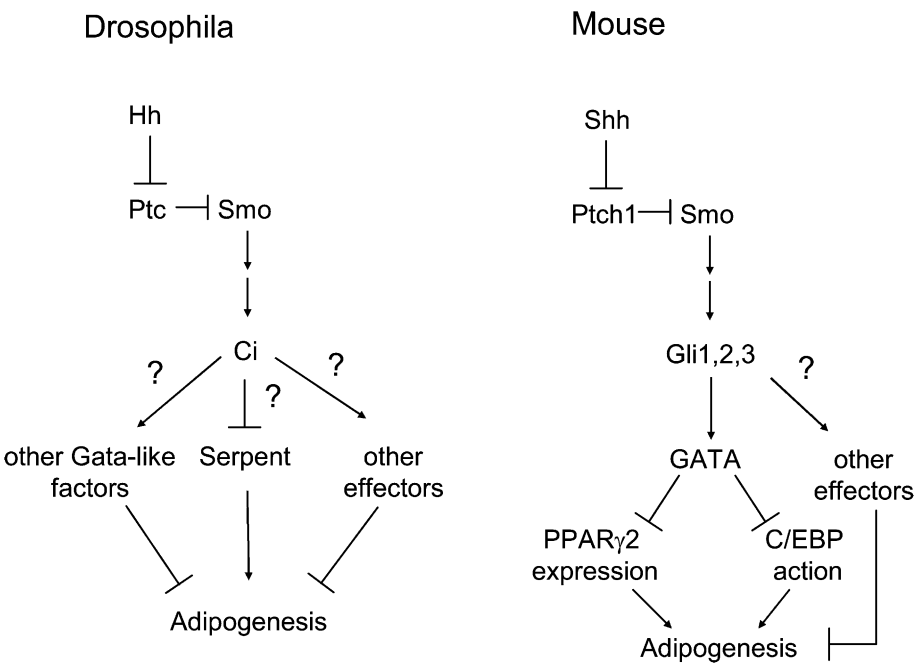


**Figure 1.** Functional relationship between Hh signaling in fat body development in *Drosophila* (left) and adipogenesis in mammalian cells (right)

In flies, Hh binds to Ptc, thus releasing Smo from inhibition. A series of intracellular events results in activation of the Ci transcription factor, which inhibits fat body development via an unclear mechanism. Some possibilities are shown, including inhibition of the proadipogenic GATA-like factor Serpent. Alternatively, Ci could activate an antiadipogenic GATA-like molecule (if one exists), which would make the system analogous to mammalian cells. In mammals, Shh activates the Gli family of transcription factors, which either directly or indirectly activate antiadipogenic GATA factors. GATA2 and 3 have been shown to repress the PPARγ2 promoter and to inhibit the function of C/EBP proteins through a direct interaction. In both flies and mice, other pathways remain possible as well.

in flies and mammalian cells, lending credence to the idea that invertebrates can be useful models for adipogenesis. Third, it suggests that drugs designed to manipulate hedgehog signaling *might* have utility in human metabolic diseases of altered adiposity, such as obesity and lipodystrophy.

This last point bears closer analysis. Could Shh agonists be used to treat obesity? Though seemingly obvious—anything that causes fewer fat cells should reduce weight gain and its adverse sequelae—this is, however, not necessarily so. Fat cells provide a sink for calories, buffering excess nutrients in a "safe" environment. As long as food intake exceeds energy expenditure (an all-too-common scenario in our society), those extra calories have to go somewhere. If adipogenesis is inhibited, they end up as ectopic lipid deposits in places like muscle and liver, which may itself cause significant insulin resistance. Certainly fatty liver is a well-known precursor to cirrhosis. The "problem" in obesity is energy balance that is out-of-whack, and not a surfeit of adipocytes per se.

Furthermore, activation of hedgehog signaling might have effects on other tissues that could impact upon body weight (even leaving aside the expected prooncogenic effects). For example, mice with a constitutively active hedgehog pathway are heavier than littermates, not lighter (Makino et al., 2001). The same effect has been seen with an injectable hedgehog agonist (Martin et al., 2002), and anti-hedgehog therapy protects against diet-induced obesity (Buhman et al., 2004). The reasons for this are unclear but may reflect general changes in cell proliferation (Makino et al., 2001), altered lipid transport in the intestine (Buhman et al., 2004), or the positive effect of Shh on insulin transcription in pancreatic β cells (Thomas et al., 2000). Regardless of the mechanism, these results are obviously discordant with the notion of using systemic Shh therapy to treat obesity. One interesting possibility is the use of hedgehog agonists for osteoporosis. Like C3H10t1/2 cells, marrow stromal cells in vivo can be induced to become adipocytes or osteocytes; during aging, the former predominates over the latter. Drugs that mimic the actions of Shh might tip the balance back to bone formation.

Regardless of the therapeutic implications, the paper by Suh et al. will stimulate the adipogenesis community to incorporate hedgehog signaling into their thinking. There are still a number of open questions that need answers. For example, can the in vitro findings be extended to whole animals? What is the source of the Shh, and what effectors other than GATA might be involved in transducing the downstream signal? Flies and worms are particularly useful organisms for identifying such epistatic genes. Finally, can Shh signal in mature adipocytes, and, if so, what are the metabolic consequences? Suh and colleagues have put hedgehog back on the adipogenesis map. How big a piece of the map it occupies remains to be seen.

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DOI 10.1016/j.cmet.2005.12.002