

Gaining a solid grip on adipogenesis

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Abstract

Obesity is presently being combated by fitness regimens, drugs and diet. Increasing our understanding of the physiology of adipocytes, by deducing the regulatory pathways involved in lipid metabolism and all aspects of adipogenesis, will provide alternative strategies to reduce adverse problems of obesity. Research has suggested that mature fat cells may dedifferentiate to form proliferative-competent fat cell precursors. Knowledge of the dedifferentiation process will allow us to gain a solid grip on adipogenesis.

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1. Introduction

1.1. The cost of obesity

Americans are becoming obese; whether young, or old, our society is getting fatter (Flegal et al., 2002; Sturm, 2003). Obesity is associated with numerous dysfunctions, including type II diabetes and heart disease (National Task Force on the Prevention and Treatment of Obesity, 2000). The cost of obesity is staggering, making obesity the third most costly dysfunction in the American health system. Nearly 10% of the total health care expenditures in the United States have been attributed to obesity (Colditz, 1999). The cost of obesity can also be felt in other ways such as lost productivity (work days) and early death (Aronne, 2001; Colditz, 1999; Visscher and Seidell, 2001). Americans spend billions of dollars on therapists, weight loss programs, exercise machinery and dietary products in an attempt to lose weight. To

some degree, many of these may work, but Americans seem incapable of staying with any one program. Consequently, most Americans fall back to their old behaviors of consuming more energy than is expended, thereby regaining whatever weight they were initially successful in losing. A key to combating obesity is gaining insight into the regulation of the adipocyte.

1.2. Physiology of adipocytes

At the cellular level, obesity involves two different physiological components. The first, lipid metabolism, is the energy flow into or out of adipocytes (lipogenesis and lipolysis, respectively). Numerous review articles have been written summarizing the detailed components of both of these processes (Cornelius et al., 1994; Houseknecht et al., 1998; Kersten, 2001; Kokta et al., 2004; Large et al., 2004). The second physiological component, termed adipogenesis, is (collectively) the discernable cellular transitions through which a spindle-shaped fibroblastic cell proceeds, first forming a preadipocyte, then a multilocular adipocyte,

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and, finally, a mature (unilocular) adipocyte (Ailhaud et al., 1992; Fajas, 2003; Gregoire, 2001; Rosen and Spiegelman, 2000). Whereas countless scientific papers are published each year regarding both of these areas (lipid metabolism and adipogenesis), little gains have been made to either formulate an effective exogenous treatment for inducing an overall reduction in body lipid or for altering (decreasing) the cellular conversion to form adipocytes. Indeed, the majority of published articles in the adipogenesis field suggest that once a preadipocyte accumulates lipid, then the cell is a terminally differentiated adipocyte—with the only option to metabolize lipid from that point onward (reviewed in Fernyhough et al., 2005). It is interesting to note that, according to traditional thought, should additional adipocytes be required in any specific fat depot, then the fibroblast-like cells that reside in the connective tissue fraction have been proposed to be converted into the requisite number of adipocytes.

1.3. Dedifferentiation

It is unfortunate that, because of the current belief in the terminality of mature adipocytes, little research has been conducted on an alternative and potentially important area: the dedifferentiation of mature adipocytes to form proliferative-competent cells. Not only is it apparently possible for adipocyte number to increase through the activity of fibroblasts/preadipocytes, but a limited number of scientific observations exist in the literature to suggest that mature adipocytes may dedifferentiate to form proliferative-competent cells (Adebonojo, 1975a, 1975b; Canello et al., 2005; Fernyhough et al., 2005; Justesen et al., 2004; Sugihara et al., 1986, 1987, 1988). It is our belief that this new area of research may provide several potentially new targets for weight loss. It might be possible to devise pharmacological treatments to induce mature cells to revert back to proliferative-competent cells. Once the cells resemble the lesser differentiated cell form, it may then be possible to devise a treatment to terminate the cells, thereby disallowing further fat storage by the cells. Alternatively, there may be devised a regimen to disallow the mature fat cells to proliferate (at all), thereby decreasing the fat cell number that might be capable of accumulating lipid. In both instances, there would be a net decrease in the cells responsible for lipid storage. Further, as the progeny of proliferative-competent mature adipocytes themselves have received little attention, we suggest that deciphering the “plasticity” characteristics of these daughter cells may lead to greater advances in our current idea of “traditional” adipogenesis. Indeed, our collaborative efforts have resulted in a repeatable method to purify mature adipocytes, documentation of the cells as they dedifferentiate, and initiation of experiments to determine the ability of progeny cells to re-differentiate into lipid-filled adipocytes (Fig. 1). This phenomenon of reverse adipogenesis by mature adipocytes, along with progeny cell adipogenesis, will allow scientists to gain a new and solid grip on adipogenesis.

1.4. Alternative possibilities

As we are observing the physiology of cells in vitro, we must allow for a bit of caution in our results. For example, might there be different explanations for the dedifferentiation seen in our cultures? From a traditional view, mature adipocytes are incapable of dedifferentiating, or even returning to proliferative competency. As we have documented, mature, lipid-laden adipocytes do initiate proliferation and do form daughter cells (many of which possess equal amounts of lipid, whereas others display asymmetrical distributions of lipid). One possible explanation for the dedifferentiation and subsequent proliferation may actually be that some fibroblast-type cells have the ability to accumulate lipid, but not to terminally differentiate. Similarly, what we have long-thought regarding the developmental potential of preadipocytes may need some revision. Preadipocytes may be capable of both proliferation and lipid metabolism—without terminal differentiation. Thus, despite the seemingly outward mature appearance of these two cell types, they may be capable of retaining their ability to return the proliferative mode when required. Lastly, what may seem to be a fully committed mature adipocyte may, in fact, represent a cell that we do not fully understand—a cell type that is able to express both differentiated and proliferative phenotypes. Regardless of the true nature of these cells, the traditional definition of adipocyte cell commitment may need to be revised in order to gain a solid grip on the complete picture of adipogenesis.

Another caveat that must be taken into consideration is the in vitro environment in which the dedifferentiation of mature adipocytes has been recorded. At best, in vitro conditions are not in vivo conditions, and the artificial milieu in which these cells are cultured must be critically evaluated. One criticism of the dedifferentiation research has been that cultured cells are not supplied with all the required nutrients for survival in a differentiated state—in essence, the cells are “starved.” However, the medium used in vitro to induce the dedifferentiation of mature adipocytes is medium that is classically referred to as “growth” medium (Cousin et al., 1999; Gamou et al., 1990; Sugihara et al., 1987, 1986). This implies that the medium contains sufficient nutrients to induce proliferation of cells—a process known to have a high requirement for energy and other metabolic building blocks. Another potential criticism of this type of research is that mature adipocyte cells have been removed from their three-dimensional in vivo environment and placed in two-dimensional plastic cell cultureware. When placed in a three-dimensional culture environment, mature adipocytes exhibit dedifferentiation in a similar manner to that in Fig. 1 (Sugihara et al., 1988).

In summary, we are proposing that alternative treatments of dysfunctions such as obesity may involve defining the regulation of a new, and more complete, version of adipogenesis. If mature adipocytes dedifferentiate and divide the resulting daughter cells will then proceed to differen-

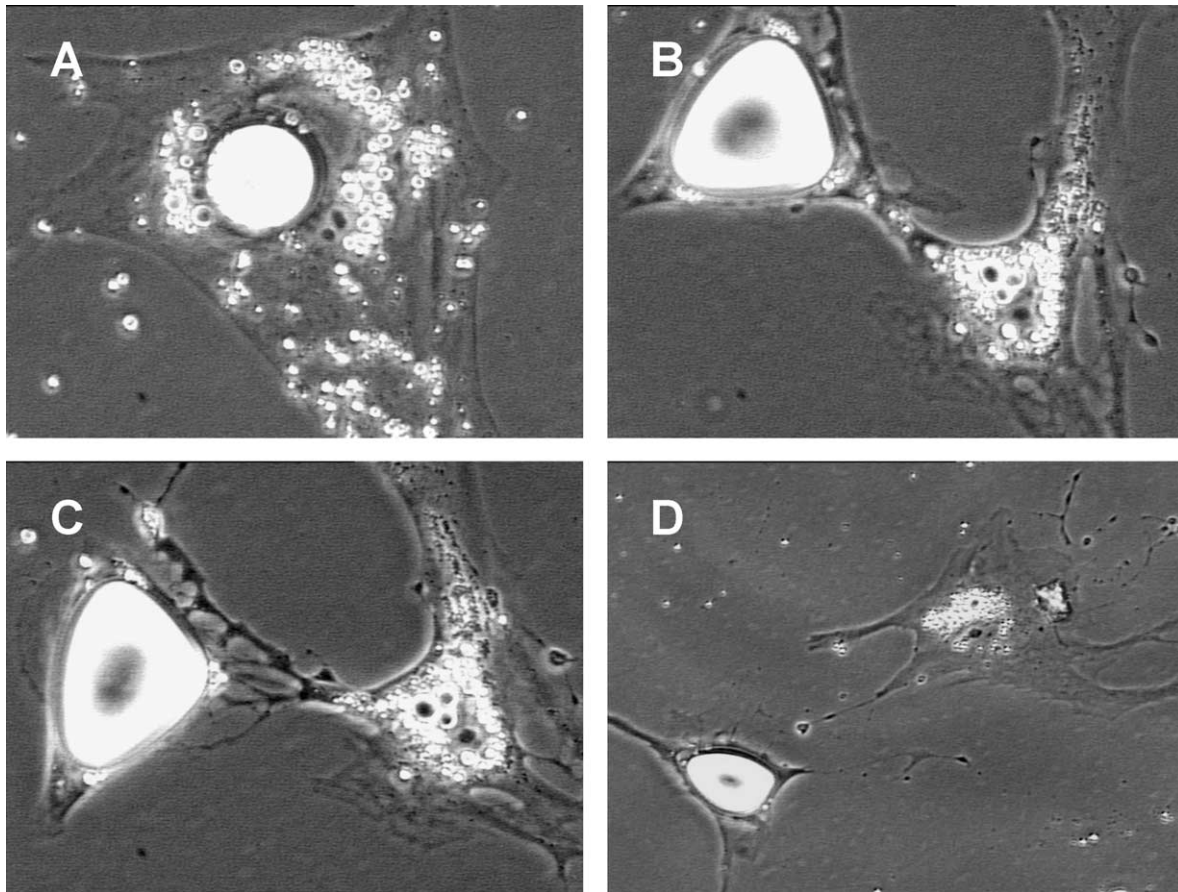


Fig. 1. Photomicrographs of a mature lipid-containing adipocyte asymmetrically dividing into proliferative-competent cells. Panel A shows a purified mature adipocyte in culture two days after a differential plating (200 \times). Five days after purification (panels B and C) the cell is actively dividing into two cells. The photomicrographs were taken 3 h apart at 200 \times magnification. Panel D shows the resulting daughter cells (100 \times) from the cell in panel A. The large lipid drop in the parent cell can be easily followed to one of the daughter cells.

tiate into a greater numbers of mature adipocytes. If this subsequent differentiation (and accumulation of lipid) is not controlled, this may be an associative factor in making one fatter. Experiments with mature adipocytes (or whatever they are determined to actually represent) may provide a new strategy for regulation of the cellularity (or metabolism) of cells capable of being involved in adipose tissue formation and growth.

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