

Assessing a Non-Traditional View of Adipogenesis: Adipocyte Dedifferentiation – Mountains or Molehills?

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Key Words

Adipofibroblast · Cell division · Obesity · Plasticity

Abstract

Based on our studies we propose the following hypothesis: mature, lipid-containing adipocytes possess the ability to undergo symmetrical or asymmetrical cell division, without losing lipid. While our research to discern the mechanism(s) involved in what we have termed ‘dedifferentiation’ of adipocytes is ongoing, we have identified several roadblocks to our work in this area. However, due to the newness of this research, we believe that none of these problems discounts the potential importance of our initial observations, or the excitement of contributing knowledge in the area. In this manuscript we address some of these problems and suggest possible solutions in an attempt to make ‘molehills’ out of ‘mountains.’

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On several occasions, we have described the ability of lipid-containing adipocytes, obtained from the subcutaneous fat depot in beef cattle, to proliferate in vitro [Dodson et al., 2005; Fernyhough et al., 2005a, 2005b, 2005c]. We have termed this physiological transition, adipocyte dedifferentiation [Vierck et al., 1996] into adipofibro-

blasts [Vierck et al., 1996]. The plasticity of progeny cells to re-form lipid-containing adipocytes or other cell types is presently being evaluated by us [Dodson et al., 2005; Fernyhough et al., 2005a, 2005b] and others [Zhang et al., 2000; Justesen et al., 2004; Canello et al., 2005]. We think that this may prove to be an emerging area of cell physiology and may amend present thinking about tissue renewal capabilities. However, this research focus is not without its problems, which will need to be rectified prior to suggesting definitively that the classical idea of the terminally differentiated state of adipocytes needs revision.

One such research problem that will need to be experimentally corrected is our analysis of cells derived from only one depot (subcutaneous) of adipose tissue rather than from other body depots. This observation stems from work demonstrating multiple differences between the regulation and cellularity of adipose depots [Vidal, 2001; Ren et al., 2002; Tchkonina et al., 2002; Altomonte et al., 2003; Laplante et al., 2003; Oliver et al., 2003; Arvidsson et al., 2004; Dicker et al., 2004; Van Harmelen et al., 2004; Rodriguez et al., 2004; Schoof et al., 2004; Tan et al., 2004; Berndt et al., 2005; Boucher et al., 2005; Giorgino et al., 2005; Hishikawa et al., 2005; Pujol et al., 2005; Rodriguez-Cuenca et al., 2005; Ross et al., 2005; Tchkonina et al., 2005]. While we are aware of these differences, the reasoning behind the use of one depot, pres-

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ently, is twofold. The subcutaneous depot in the beef animal is the largest and easiest depot from which to remove adipose tissue during slaughter. Additionally, while there exists some preliminary evidence that adipocytes isolated from other fat depots possess a similar ability to dedifferentiate in vitro [Sugihara et al., 1986, 1987, 1988; Shigematsu et al., 1999; Justesen et al., 2004; Canello et al., 2005], the focus of the previous work cannot address the specific population dynamics of mature adipocyte dedifferentiation. Consequently, while we would like to extrapolate our work to other adipose depots, we will not be in a scientific position to do so until we have actually performed a careful study of cells derived from other depots.

Another problem that will need to be resolved is the suggestion that we are looking at cell physiology transitions in an abnormal in vitro environment. In other words, is the dedifferentiation that we observe an artifact of the two-dimensional cell culture system being employed? Further, would such physiologic reversion ever occur with mature (differentiated) adipocytes in vivo? The closest culture environment to that experienced by adipocytes in vivo is the three-dimensional culture system [Sugihara et al., 1988; Shigematsu et al., 1999], which has similarly showed results suggesting that dedifferentiation of unilocular adipocytes may occur. However, in all cell culture systems, there is no blood supply, nervous interaction or exposure to all of the chemical mediators that mature cells may be exposed to in vivo. Consequently, our observation may be relegated to the in vitro environment, only. However, even if the dedifferentiation process only occurs in vitro, such a system would provide knowledge of the regulation of such events that might be (eventually) useful in alleviating the problems associated with the general accumulation of excess body fat. The elucidation of similar cell reversions occurring in vivo must wait until we have generated cellular assessment tools (markers) that might be employed in either in vivo or, possibly, in an in situ system.

A further possible drawback with our cell culture system is that, despite the constant exposure of the adipocytes to classical, high-serum growth medium (10%), we may be starving the cells of some component present in vivo; consequently they have no recourse but to lose some lipid and divide in vitro. We propose that a 'starving' adipocyte would do one of three things: remain in the same physiological state, utilize the intracellular lipid stores for energy (delipidation), or undergo apoptosis. Many of the dedifferentiating adipocytes do so without losing lipid [Dodson et al., 2005; Fernyhough et al., 2005a, 2005b,

2005c]. However, we are constantly evaluating our in vitro environment for the presence/absence of regulators and metabolites required to maintain cell health.

Because adipose tissue contains different populations of cells, there may be a chance that our cell cultures never achieve the purity required in order to convince anyone of the homogeneous nature of the cell population. Whereas this observation may hold true with earlier observations [Adebonojo, 1975a, 1975b; Van et al., 1976; Sugihara et al., 1986, 1987, 1988; Shigematsu et al., 1999], recent work on methods to purify the primary adipocyte cultures in our laboratory, as well as in at least one separate laboratory, has led to remarkably similar procedures and results [Fernyhough et al., 2005c; Tholpady et al., 2005].

Our observations to date, albeit descriptive, lead us to several possible explanations regarding possibilities for adipocyte dedifferentiation. First, mature fat cells may not necessarily be fully differentiated cells and may actually be preadipocytes, adipofibroblasts, or fibroblasts that possess the ability to assimilate large quantities of lipid while remaining non-differentiated adipocytes. Previous research has demonstrated that normal preadipocyte differentiation into lipid-laden mature adipocytes can be depot dependent [Shigematsu et al., 1999]. Why, then, is it not possible for some of these cells to contain lipid, but not be fully differentiated? This is for additional research to elucidate, and may actually be the physiology at play in our observations. A second possibility is that these cells are more 'stem-cell-like' and that they not only are able to proliferate but might be more 'plastic' and have the ability to form other cell types (e.g. myocytes, chondrocytes or osteocytes) [Justesen et al., 2004]. Lastly, the possibility exists that we have identified a cell type residing in adipose tissue that may be an entirely new cell of the mesodermal lineage. Regardless of the determination of the final cell type, we believe that knowledge of the regulation of the dedifferentiation event, in vitro, will add to our understanding of adipose tissue biology.

We are excited to bring this research area to the attention of others. By so doing, regardless of present barriers, we hope to encourage other researchers to commit adequate personnel and resources to focus on this potentially vital (but relatively ignored) part of adipocyte physiology – the ability of 'mature' adipocytes to retain their ability to proliferate. We consider this research relevant for a number of human medical diseases including obesity, diabetes, lipodystrophy, and hypertension.

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