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BRIEF REPORT

Potential Impact of Mature Adipocyte Dedifferentiation in Terms of Cell Numbers

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Mature adipocytes possess the capability to dedifferentiate and form proliferative-competent progeny cells. Little is currently known about the daughter cells, or the impact of such *in vitro* physiology in an *in vivo* situation, and the daughter cells may actually represent cells with stem-like cell potential. The present paper introduces implications of and impact of this physiology in terms of animal adiposity and composition.

Keywords: Adipocyte, Dedifferentiation, Stem cells, Domestic meat animals, Composition, Growth and development

Adipose tissue accumulation is associated with obesity, insulin resistance and many other metabolic diseases. In animal production, excessive adipose tissue deposition reduces feed efficiency and leads to waste (1). Adipose tissue is a dynamic tissue, and from a cellular perspective, some adipocytes in adipose tissue depots die and are replaced with new adipocytes (2). In general adipose depot-specific hyperplasia may occur into adulthood (3). A key question is where do these new adipocytes come from? The classic view is that these cells are derived from the precursor cells in the connective tissue fraction of adipose tissue (4), and recently bone marrow stem cells in circulation are confirmed as a significant contributor to new adipocytes in adipose tissue (5, 6). Here, we propose that the dedifferentiation of mature adipocytes and daughter cell proliferation constitutes another significant source of new adipocytes.

In basic terms, development is formally comprised of two different parts: determination (the range of cells that any one cell may form) and differentiation (proceeding from a lower to a higher level of complexity, and being composed of determination, morphogenesis, maturation and senescence. From a traditional view, then, mature adipocytes are incapable of dedifferentiating, or even returning to proliferative competency. But they do.... and more and more people are realizing the potential significance. For example, we have previously shown that mature adipocytes from both ruminant animals like beef cattle (7-10) and monogastric animals like pigs (11, 12) possess ability to dedifferentiate (7-10, 13, 14) and from proliferative competent progeny cells *in vitro* (7, 10-12). These cells are capable of undergoing population expansion (10), and may re-differentiate to form lipid-filled adipocytes (7, 10-12). Potential of the progeny cells to form other cell types (15, 16) is presently being examined. Collectively, significant unto itself, this system provides an alternative system to stromal vascular cells and cell lines to examine variables of adipogenesis and lipid metabolism (11-13, 15, 17-20). However, it still needs to be determined whether mature adipocytes possess similar capability to perform such actions *in vivo* (1). Moreover, considering the ramifications of such occurring, would such a physiological event make any impact on adipose depot size and amount?

Drawing from previously published papers, it is possible to speculate on the contribution of adipocyte dedifferentiation/redifferentiation on overall adiposity. Such

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might provide some impetus for others to enter into this area of research and facilitate uncovering answers to this (potentially) important area. Classic research showed that specific numbers may be assigned to different adipose depots in beef cattle throughout postnatal aging (3). Moreover, the total amount of adipose tissue (in kg) has been determined on an animal and adipose tissue depot basis (3). Fernyhough et al. (7) proposed that 1 cell out of every 100 mature adipocytes possessed the ability to dedifferentiate and form proliferative-competent progeny cells *in vitro*. Presently, no established estimate of overall (lifetime) proliferative capacity has ever been established for the progeny cells, but Webster et al. (21) proposed that 10^4 myogenic satellite cells can be obtained from 0.1 g of muscle tissue, and that these (isolated) cells may produce 1 kg of new cells. Should the adipose tissue-derived mature cells possess similar cellular characteristics, then the effects of adipocyte dedifferentiation/redifferentiation may account for a significant amount of adipose tissue hyperplasia into adulthood of animals. For example, in the subcutaneous adipose depot of 19 month old beef steers (alone) there exists 43.2 kg of tissue and 14.306 billion cells (3). Should, in fact, 1/100 mature adipocytes possess the ability to dedifferentiate and form proliferative-competent progeny cells, then approximately 100 million of the cells are potentially capable of forming new adipocytes, or other types of cells, if subjected to the appropriate physiological regulation.

The possibility that almost every cell type in the adipocyte lineage, including mature adipocytes, are capable of proliferation and differentiation affords a great potential to very adipocyte-filled tissues, and supersedes the traditional idea that new cells added to any adipose depot are only from preadipocytes, adipofibroblasts, or (as yet) undefined stem cells residing in the depot (7). This research needs to be resolved (15). Animal influences on cell physiology, and depot-specific regulation differences must be included in any research design. However, the potential of outcomes of this research being applied to animal growth and development, human health and dysfunction resolution and alleviating the adverse effects of aging on body composition make the research area ripe for much participation. Indeed, the potential impact of mature adipocyte dedifferentiation in terms of cell numbers may benefit new modalities such as tissue regeneration, may change current ideas regarding postnatal stem cells, and may be useful in a variety of applications of tissue engineering (16).

Potential conflict of interest

The authors have no conflicting financial interest.

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