Adipose depots differ in cellularity, adipokines produced, gene expression, and cell systems

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The race to manage the health concerns related to excess fat deposition has spawned a proliferation of clinical and basic research efforts to understand variables including dietary uptake, metabolism, and lipid deposition by adipocytes. A full appreciation of these variables must also include a depot-specific understanding of content and location in order to elucidate mechanisms governing cellular development and regulation of fat deposition. Because adipose tissue depots contain various cell types, differences in the cellularity among and within adipose depots are presently being documented to ascertain functional differences. This has led to the possibility of there being, within any one adipose depot, cellular distinctions that essentially result in adipose depots within depots. The papers comprising this issue will underscore numerous differences in cellularity (development, histogenesis, growth, metabolic function, regulation) of different adipose depots. Such useful information is useful in deciphering adipose depot involvement both in normal physiology and in pathology. Obesity, diabetes, metabolic syndrome, carcass composition of meat animals, performance of elite athletes, physiology/pathophysiology of aging, and numerous other diseases might be altered with a greater understanding of adipose depots and the cells that comprise them—including stem cells—during initial development and subsequent periods of normal/abnormal growth into senescence. Once thought to be dormant and innocuous, the adipocyte is emerging as a dynamic and influential cell and research will continue to identify complex physiologic regulation of processes involved in adipose depot physiology.

Introduction

The study and the behavior of fat has led to the classification of adipose depots (AD) in several different ways (Table 1). One way to categorize AD would be to define them in relation to the nearby tissues such as: splenic, hepatic, cardiac, inguinal, abdominal, and pericardial fat. Also, the morphology of the depots may be a means of differentiation between “brown” and “white” adipose tissues (BAT and WAT respectively) and are somewhat based on differences in adipocyte mitochondrial content. Regardless of differences in anatomical location, description, and cellular characteristics, all AD share several common underlying features including blood vasculature and the presence of various non-lipid storing cell types that are depot specific. In addition, AD have the ability to increase or decrease in cell size and number and in the cellular ability to metabolize lipid which partly depends on depot cell composition. Another feature of AD is the synthesis and release of chemical regulators (adipokines) that regulate within the AD, adjacent cells, or systemically with different AD having different adipokine profiles. The dynamic structure and function of adipose tissue is reviewed with a particular focus on large animal and human knowledge.

In meat-type animals, mesodermal stem cells are directed to form preadipocytes during embryonic and fetal development. A limited number of discernible AD may be visualized during late embryogenesis such that distinct patterns of development of AD and adipose tissue formation have been described and can be compared with more-studied patterns in newborn rats. In summary, these studies suggest there is a spatial and temporal relationship at the onset of adipose development which includes a relationship to vasculature. Several regulators, such as maternal nutrition, are linked to the specialization of the mesodermal transition. In humans, epidemiological studies have linked maternal under- and over-nutrition to increased adiposity and other health problems throughout the life of the offspring. In food animals, a dramatic increase in AD cellularity starts at weaning and peaks during the finishing period. Regulation of cell proliferation or differentiation during all stages are likely to include cellular genetics (intrinsic regulation), growth factor and nutrient availability (extrinsic regulation), influences of other cells within the AD (chemical and physical regulation), and interplay among adipose lineage cells and other cells from outside/inside the AD such as immune cells.

There does not appear to be one developmental moment where AD cellularity might be adjusted/regulated to ensure proper “fattiness”, as the cellulartiy of all AD are under constant alteration throughout one’s lifespan. A recent study explored dynamic changes of the adipose tissues by characterizing adipocyte differentiation in various depots (during development) using...
Table 1. Differences among adipose depots of domesticated (meat) animals

| Differences                      | References |
|----------------------------------|------------|
| Animal                           | 36–39      |
| Gender                           | 22 and 40–48 |
| Breed                            | 49         |
| Species                          | 38 and 50–54 |
| Cell (number, differentiation ability, etc.) | 24, 36, 41, 42, 53, 55, 56, 59, and 62–66 |
| Lipid metabolism (preference for fatty acids, etc.) | 35, 38, 39, 49, 51, 54, 57–59, 65, and 67–69 |
| Adipokine/chemokine Types/amounts | 46, 48, 70–74 |
| Longevity/aging                  | 45, 51, 63, and 75 |
| Response to endocrine agents     | 46, 74, and 76 |
| Insulin                          | 24, 46, 39, 55, 56, and 74 |
| Growth hormone                   | 66, 74, and 76 |
| Steroids                         | 24, 36, 53, 55, 56, and 62 |
| Adrenergic compounds             | 47, 74, and 76–79 |
| PPAR-agonists                    | 24, 56, 61, and 75 |
| Response to nutrition (feeding regimen/diet) | 29, 37, 42, 47, 62, 74, 77, and 80–86 |
| Gene/protein expression          | 1, 21, 23, 29, 39, 43, 44, 52, 56, 60, 61, 64, and 81 |
| Among depots                     | 22, 35, 40, 45, 57, 58, 63, 87, and 88 |
| Within a single depot            | 71, 72, 74, and 89–101 |

Gene expression differences have been described in preadipocytes, adipocytes, and adipose tissue. Preadipocyte expression profiles of genes involved in cellular stress and regulation of differentiation differ extensively among epididymal and perirenal fat depots in mice and humans. In humans and rodents, two main types of WAT (SC and VIS fat) and BAT show differences in adipokine secretion, insulin sensitivity, and lipolysis rate that are correlated with differences in expression of developmental and patterning genes between adipocytes in different depots. Developmental and adipogenic gene expression displayed a unique pattern in two SC and three intraabdominal WAT depots as well as BAT from lean or obese mice regardless of whether they were in a fed or fasting state. Visceral adipocyte cells showed higher levels of expression of GATA2 and transforming growth factor β, factors known to inhibit adipogenesis, whereas SC adipocyte cells showed higher expression of pro-adipogenic genes including peroxisome proliferator-activated receptor gamma (PPARγ). Differences in gene expression profiles and related functional networks have associated the cytokine release ability to the anatomical origin of adipose tissue-derived stem cells in humans. Genome-wide profiling of PPARγ in primary epididymal, inguinal, and brown adipocytes revealed the depot selective binding of PPARγ that results in the induction of genes characteristic of different adipocyte lineages. It is important to emphasize that cell population heterogeneity or exposure of cells to complex microenvironments can lead to differential gene expression in only a subpopulation and any study of gene expression will unavoidably average out differences between subpopulations. Single cell genomic approaches will undoubtedly help

the AdipoChaser mouse. By crossing adiponectinP-rtTA (adnP-rtTA) transgenic mice with TRE-cre and Rosa26-loxP-stop-loxP-lacZ transgenic mice, mouse lines were developed that can be induced to permanently label their mature adipocytes. These cells could then be followed over time. Results from this study, in part, suggested that subcutaneous fat development begins between embryonic days 14 and 18 while gonadal fat develops postnatally. Moreover, when lipid deposition was stimulated by feeding the mice a high fat diet, adipogenesis in epididymal fat began after 4 wk and subcutaneous fat sustained hypertrophy for up to 12 wk. These results highlight the extensive differences in adipogenic potential in various fat depots and supports extensive results in several species that describe differences among AD. Consequently, it may be useful to treat each different adipose tissue depots as a separate “miniorgan” due to the variation of timing and rates of adipogenesis.

As previously mentioned, AD contain a variety of cell types. Although the cellularity of different AD may be consistent with respect to the types of cells present, depots can be inconsistent with respect to the numbers of cells residing in any specific cell population. Individual cell populations may also differ between adipose tissue depots as reflected in the types of genes expressed and subsequent protein markers discernible in studies to date. In fact, progeny cells isolated from different AD still retain those differences many generations later. This is critical for study design and data interpretation. For example, studies are often designed to assess functional differences among AD after isolating cells from various depots and evaluating them in vitro. Although functional differences are frequently reported, simply showing that cells do something, in vitro, when they have been isolated from an AD during physiological transition is not sufficient. This is because it is well established that cells within AD are not all at the same stage of development and assuming that they are by not assessing the cell subtypes will inevitably lead to incorrect conclusions. The cellularity and composition of individual AD must be evaluated prior to making assumptions about the regulation potential of a depot. This can be illustrated by the following example. Individual one has 10,000 adipocytes while individual two has 2000 adipocytes within a specific AD. These adipocytes are capable of producing gene product X. These adipocytes differ in efficiency of producing gene product X resulting in equivalent/more/less of the same gene product. Thus it is possible to see the same/more/less of gene product X from a vastly different number of adipocytes but cause confounding results when determining a role of an adipocyte, AD, and adipokines on the systemic health of an individual. It is more appropriate to characterize the cells and their depot of origin to understand how the efficiency of producing gene product X is being altered.
identify gene expression patterns, genomic variants, or QTLs from single cells, which could allow for improved assessment of the genotype-phenotype connection in heterogeneous cell populations. Distinct profiles of gene expression and protein changes have been observed between adipocytes derived from different AD in both pigs and beef cattle.21-24 Subcutaneous and VIS preadipocytes showed differential expression of CCAAT enhancer binding proteins (C/EBP), an important family of transcription factors involved in establishing insulin sensitivity during the regulation of adipocyte differentiation, carnitine palmitoyl transferase 1B and fatty acid binding protein 4 during differentiation.25 In cattle, the dietary roughage content of the feed was related to differential expression of the adipogenic transcription factor C/EBPβ in SC and IM adipose tissue.26 Other studies indicate that fat depot-specific differences in angiogenic growth factor gene expression could result from the difference in adipocyte size since intermuscular, renal, and mesenteric adipose tissues expressed significantly higher vascular endothelial growth factor, fibroblast growth factor-10, and leptin mRNA levels than did SC and IM adipose tissues.27,28 Recent studies in beef cattle have established the differential expression of microRNAs, endogenous non-coding RNA, between fat depots and with different dietary intake offering the possibility that microRNAs may be a molecular mechanism regulating site-dependent adipogenesis.29,30

**Adipokines**

It is generally accepted that individual endocrine-releasing cells are present in various tissues throughout the body. A well-established example of this is the I-cell of small intestine epithelium. I-cells release considerable numbers of endocrine and paracrine agents that regulate diverse physiologies such as acid production in the stomach, small intestinal smooth muscle contractions, and cholecystokinin release, which may play a role in satiety at the level of the brain. More recently, the paracrine and endocrine secretions of adipose tissue have been described. These adipose tissue secretions are known to release a variety of chemical agents, which interact with other adipocytes/cells of specific—but not all—AD, immune cells, and somatic cells distant from the adipose depot. While some of the secretions from adipose tissue may be from non-adipocyte cells including fibroblasts, vascular cells, etc., others are secreted from adipocytes and are thus classified under the group name adipokines. The very knowledge of adipokine release by AD raises several questions. Do all AD release endocrine-like regulatory agents and what is the regulation? For those AD containing secretory adipocytes, are these adipocytes similar to secretory cells seen in endocrine glands and are there secretion variables including a “master” regulator that induces adipokine release? In order to define this potential regulator or another, the general pattern of adipokine release might be examined. For example, diurnal release patterns commonly observed with GH release in humans, or episodic release observed with IGF are both characteristic patterns that could be expected. In fact, characteristics of leptin secretion in pigs indicated that the frequency and amplitude of leptin pulses were subject to physiological factors such as fasting.31 Are secretion patterns regulated by the associated sympathetic nerves at the level of the individual adipocyte or by adipose tissue section that may or may not release a specific adipokine? Could this relate to developmental gradients within a depot that could include the associated developing innervation, vascularization, and (then) cells? This may serve to imply area-specific developmental differences in regulation of the cells residing in adipose depots. A myriad of questions remain but it is clear that the release of adipokines must be thoroughly defined in order to reflect a common/divergent pathway of endocrine agent synthesis and release from individual adipocytes.

**Adipose Cell Systems**

A variety of cell systems are available to study aspects of adipocyte proliferation, differentiation, dedifferentiation, transdifferentiation, and adipokine release. Most of the information known about preadipocyte proliferation, conversion from proliferation to differentiation, and initiation/maintenance of lipid metabolism is based on studies with cell lines and stromal-vascular (SV) cell systems that rely on non-lipid bearing cells from an adipose tissue isolate to initiate studies. SV cells will retain characteristics conveyed from the AD from which they were isolated providing valuable information.1,11,12 However, the data are limited to adipogenesis and lipid metabolism from that specific AD and may not predict overall adiposity or what could be observed in other AD. Emerging cell culture systems from an adipocyte lineage in vivo include adipose stem cells found in postnatal tissue, ceiling culture of mature, lipid filled adipocytes used in cell dedifferentiation studies, and cultures of bone marrow cells transdifferentiated into adipocytes. Adipose tissue cells have great potential for isolation of stem-like cells and subsequent use in tissue remodeling/regeneration applications.32,33 Some technical and physiological difficulties exist in most of these in vitro systems, however. Cell line culture systems use transformed cells, suggesting a non-physiologic immortality of the cells. Cell culture systems using SV cells contain multiple populations of cells with unknown proportions, disallowing consistency among experiments. Moreover, in both cell line and SV systems, there is a clear non-uniform response, suggesting that 100% of cells never perform similarly. Recent studies demonstrated that the preadipocytes isolated from mouse inguinal SC AD actually contain two distinct adipose cell types: beige fat cells and white fat cells.34 These two cell types exert different cell structure and genes expression profiles and may be a reason that less than 100% of the cells will differentiate. It is problematic to extrapolate useful results from the data unless one knows the specific proportion of cells within the cell isolates used for in vitro studies.

Current cell systems for defining aspects of AD cellularity cells rely on methods/regimens that are not present within physiological tissues. For example, proliferative-competent cells in vitro require exposure to a “differentiation cocktail” for a period of
time. This cocktail is commonly composed of dexamethasone (DEX), methylisobutylxanthine, and insulin (IBMX) and applied for up to 48 h to conferunt cell cultures (also not physiologic) to provide intracellular signaling moieties that overload differentiation mechanisms and induce cellular conversion. After 48 h exposure, DEX and IBMX are removed and insulin begins to induce the incorporation of lipid. However, this lipid assimilation phase may take weeks in vitro. In addition, the IBMX “differentiation cocktail” may contain additional ingredients that differ between researchers, such as fatty acids or a second corticosteroid, to speed up the process of adipogenesis. Consequently, using cell cultures for the main experimental model requires considerable time for preparation, conduct, and analysis. Individual in vitro systems may work for a specific purpose, but the same system may be useless for a different aspect of adipocyte physiology among different AD. Recently, the differentiation cocktail has been very much simplified for primary cultures of ovine, murine, and bovine cells.

**Summary/Conclusions**

Adipose depots may possess divergent cellularity, but the differences within individual depots or specific cell populations within a specific depot may be greatly different. To date, it appears that gene expression, microRNA, DNA methylation, and association with neural and vascular cells may regulate adipose tissue secretions and function. Technologies such as single cell analyses and cell sorting leading to evaluation of specific, and identifiable, cell populations will allow for better understanding of gene expression and secretions of factors from various cell types found within adipose tissue. Today, we are concerned about differences in AD, but in the future we may be studying clusters of adipocyte-type cells within a specific adipose depot akin to an adipocyte depot within an adipose depot.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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