Quantitative dynamics of adipose cells

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Adipose cells are unique in the dynamism of their sizes, a requisite for their main function of storing and releasing lipid. Lipid metabolism is crucial for energy homeostasis. However, the regulation of lipid storage capacity in conditions of energy excess and scarcity is still not clear. It is not technically feasible to monitor every process affecting storage capacity such as recruitment, growth/shrinkage and death of individual adipose cells in real time for a sufficiently long period. However, recent computational approaches have allowed an examination of the detailed dynamics of adipose cells using statistical information in the form of precise measurements of adipose cell-size probability distributions. One interesting finding is that the growth/shrinkage of adipose cells (> 50 μm diameter) under positive/negative energy balance is proportional to the surface area of cells, limiting efficient lipid absorption/release from larger adipose cells. In addition to the physical characteristics of adipose cells, quantitative modeling integrates dynamics of adipose cells, providing the mechanism of cell turnover under normal and drug-treated conditions. Thus, further use of mathematical modeling applied to experimental measurements of adipose cell-size probability distributions in conjunction with physiological measurements of metabolic state may help unravel the intricate network of interactions underlying metabolic syndromes in obesity.

Introduction

Organisms that maintain body temperature homeostatically by internal processes, heating or cooling, are able to function in a broad range of external temperatures. While this is apparently a considerable advantage as a survival strategy, it requires the maintenance of an energy store capable of buffering against the vicissitudes of weather and food supply. As the main store of energy in mammals, white adipose tissue (WAT) plays a central role in energy homeostasis. Its primary function is to efficiently store energy in the form of lipid droplets, mainly triglycerides (TG), supplying non-esterified fatty acids (NEFA) as needed. Absence of WAT leads to ectopic fat deposition in the periphery, suggesting, teleologically, that other organs have not needed to develop alternatives that allow the body to cope with dysfunction or inadequacy in WAT storage capacity. WAT dynamics, defined in this review as the hormone-mediated interplay between adipose cell growth (lipogenesis), shrinkage (lipolysis), recruitment and apoptosis/necrosis, is an intricate ensemble of processes that buffers energy supply and demand for the entire mammalian body.

WAT is constantly varying. It can expand to store excess fatty acids (FA) in the form of TG—lipogenesis—or shrink by hydrolyzing stored TG—lipolysis—to provide energy under fasting conditions. WAT expansion occurs either by enlarging the size of the adipose cells—hypertrrophy—wherein existing cells uptake available FA, or by increasing their number—hyperplasia—wherein new adipose cells are recruited from adipose cell precursors, which in turn are differentiated from mesenchymal stem cells and undergo replication/proliferation. WAT dynamics is regulated by both external stimulation, such as hormonal (e.g., insulin from the pancreas) and neural (e.g., noradrenaline) inputs and internal stimulation (e.g., leptin produced within the adipose tissue). These factors vary depending on nutritional input, environment, genetic makeup, gender, age and location of the adipose tissue depot. It has long been recognized that the sizes of adipose cells are indicators of metabolic state. Radiocarbon dating studies on lipid and adipose cells’ age suggest a continuous shuttling of lipids between adipose cells of different sizes. Similarly, a regular turnover of both adipose cell precursors and adipose cells is observed. Aged or malfunctioning adipose cells die and are replaced by new differentiating ones such that, in healthy human adults, the total adipose cell number stays approximately constant. Comprehensive surveys of the various factors affecting WAT physiology are available. A dysfunction in lipid storage ability of WAT leads to lipotoxicity—i.e., excess fat accumulation in non-adipose tissues such as skeletal muscles, kidneys, heart, liver and pancreas—and consequently cell apoptosis, and cardiac and metabolic diseases such as cardiomyopathy, type 2 diabetes, dyslipidemia and non-alcoholic steatohepatitis. Aside from lipodystrophy, obesity is a major factor in the processes leading to lipotoxicity. A possible reason is that since there is a need to keep plasma NEFA concentrations within a safe range, an overabundance of lipids causes a redirection of the dietary fat pathway. However, not all obese individuals have the same risk of developing a metabolic syndrome. For example, insulin sensitivity varies among individuals with the same level of obesity. A better predictor is how lipid is distributed among the various WAT depots, as the latter vary in their functional properties. For example, many studies show a positive correlation between upper body obesity and cardiac and metabolic...

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Adipose cell-size probability distributions

The Couler counter serves as a useful instrument for the quantification of adipose cell size. Precise cell-size measurements reveal that adipose cell size has a roughly bimodal distribution (Fig. 1). This suggests that there may be two distinct populations of cells, and that mean adipose cell size and mean cell number may not be effective measures for summarizing the state of adipose tissue. In particular, adipose cells exhibit an enormous range in their volumes. Large adipose cells have diameters more than ten times bigger than small ones. This flexibility is directly relevant to the primary function of adipose cells: storing energy in the form of lipid. The volume of lipid stored in an adipose cell increases as the third power of the diameter. As mature adipose cells consist of a large lipid droplet surrounded by a thin cytoplasmic layer, this volume increase is almost entirely available for lipid storage. Adipose cells of diameter 200 microns contain 1,000 times the lipid of an adipose cell of diameter 20 microns.

It is not clear, however, that there is an inherent metabolic difference between small and large adipose cells. Wueest et al. measured insulin responsiveness of adipose cells of different sizes taken from the epididymal depot of mice and found no difference between small and large cells. McLaughlin et al. investigated the cell-size distribution of adipose cells taken from the subcutaneous adipose tissue of insulin-resistant and insulin-sensitive human subjects and reported that the former showed a larger population of very small cells than the latter. Furthermore, small cells isolated from Zucker obese rats were shown to have higher expression of inflammatory genes as compared with large cells, and lower levels of adiponectin and PPARγ as compared with lean rats, which may explain the lower adipose tissue lipid storage capacity in insulin-resistant individuals. Inflammatory activity was shown to be associated with insulin-resistance independent of obesity in both abdominal subcutaneous and omental visceral adipose tissue. Similarly, a higher proportion of small cells is also associated with a rise in inflammation and higher ratio of visceral to total (visceral and subcutaneous) fat. These studies did not show, however, whether the upregulation in inflammatory markers precedes the expansion in small cell population or vice versa. As insulin resistance is also accompanied with a down-regulation in adipose cell differentiation in both human and rodent subjects, one can speculate that the increase in small adipose cell population in insulin-resistant subjects must be due to proliferation. If this is true, then these new small cells might not necessarily represent mature adipose cells since the latter are generally believed to be unable to replicate; adipose cell proliferation was only observed in vitro but is yet to be shown in vivo. Alternatively, it is possible that though adipose cells do not normally replicate, they do so under extenuating circumstances, giving rise to new malfunctioning cells which, in turn, would increase inflammation further. If the malfunction is due to infiltration by macrophages, then one would expect large cells to be deficient in the uptake of fatty acids too. This, however, seems not to be the case as evidenced by the increase in the size of large adipose cells in Zucker obese rats. Clearly, small adipose cells are not inherently unable to uptake new lipids as pioglitazone treatment was shown to enhance insulin sensitivity and increase the population of small adipose cells in the human abdominal subcutaneous fat depot and the ovarian, retroperitoneal and subcutaneous fat depots of Zucker obese rats.

Studies examining the size distribution of adipose cells—as opposed to simply calculating the total cell number and mean cell size—were able to shed more light on the mechanism of adipose cell redistribution and its relation to obesity related diseases, particularly since adipose cells are not homogeneous in their ability to uptake lipids or their functional properties. Correlations may be drawn between measured physiological characteristics and attributes of the probability distributions, assuming that the state of the adipose tissue is at an approximate equilibrium with respect to the associated physiological parameters.
Our focus here is on the understanding of adipose tissue remodeling that can be gleaned from modeling the temporal dynamics of detailed adipose cell-size probability distributions. We are concerned in this review with dynamic measurements that show evolving changes in the adipose cell-size probability distributions. It is not possible to adequately fit such complex changing distributions with a small set of fitting functions as in references 36, 40, 46 and 48. Besides this inadequacy, dynamic data contains a plethora of information that should not be discarded by static fitting. The alternative is to use all the information contained in the adipose cell-size probability distributions produced by the Coulter counter and model physiological changes along with the time-evolution of the distributions. What is needed is a dynamic model that tracks the time course of the change in the adipose cell-size distribution with the progression of age and physiological inputs such as hormones, cytokines and growth factors. Current experimental techniques alone are incapable of tracking the evolution of microscopic details in vivo. Instead, one can obtain the data of interest (e.g., adipose cell-size distribution, plasma insulin concentration, etc.) at different time periods. Then, with the aid of a mathematical model, it is possible to explore the progression of events underlying the phenomenon of interest. Furthermore, such an approach allows the examination of competing hypotheses via a comparison of their likelihood values.

What questions can we answer with these fine-grained time-dependent adipose cell-size probability distributions? The appropriate questions depend on whether this data are longitudinal or cross-sectional. We focus here on what we can learn from the dynamics of adipose cell-size distributions measured at a succession of time-points. The cell-size distributions may be obtained from the same animal by means of micro-biopsies, or from animals killed at each time-point. In the latter case, it is possible to obtain absolute cell numbers from each fat location and thereby obtain estimates of the absolute adipose cell-size distribution. In the former case, the absolute cell numbers are unavailable and the analysis must be confined to easily accessible fat depots.

For dynamic changes in probability distributions, the standard mathematical tool is the Fokker-Planck equation. This equation describes the evolution of a probability distribution of a family of similar objects with a measured characteristic, in our case adipose cells with the cell-size as the measured characteristic, with respect to time as a result of processes that change the measured characteristic. Thus, in our case, the processes of interest are lipid turnover, lipid uptake, lipolysis, cell death and cell neogenesis, which manifest as cell-size fluctuations, cell-size increase, cell-size

![Figure 2. Schematic changes of cell-size distribution under various processes. Initial cell-size distribution (dotted gray line) changes with (A) recruitment of new cells at the minimal size, (B) growth and (C) shrinkage of cells, (D) fluctuation of cell size and death of cells at (E) small and (F) large size. Note that the total cell number is normalized as a unity for the initial size distribution.](image-url)
decrease, cell-number decrease and cell-number increase, respec-
respectively. Figure 2 shows how each of these processes leads to
characteristic changes in the adipose cell-size probability distribution.

To answer qualitative questions about dynamics in the adipose
tissue, it may suffice to apply Bayesian model comparison to a
variety of models suggested by the qualitative questions of
interest, and avoid parameter estimation in a Fokker-Planck
approach. Thus, for example, to ascertain if there is feedback in
adipose cell-size distribution changes that may be correlated with
additional cell recruitment, it suffices to check if there is any
periodicity in the adipose cell-size probability distributions for a
variety of possible periods.

Changes of Adipose Cell-Size Distribution

Lipid metabolism is critical for energy homeostasis. However,
specific mechanisms of lipogenesis and lipolysis in adipose cells are
not clearly understood because real-time monitoring of individual
adipose cells for sufficiently long time is not technically feasible.
As an indirect way, changes of adipose cell-size distribution have
been examined under various conditions in chick embryo
development, lean and obese Zucker rats, partially lipecto-
mized Wistar rats, and human adipose tissue. Changes of Adipose Cell-Size Distribution

Figure 3 shows changes of adipose cell-size distributions under
weight gain and loss conditions. In the weight gain condition
(Fig. 3A), total cell number increased, large cells appeared more
and a bump at the size distribution disappeared. In the weight loss
condition (Fig. 3B), total cell number decreased especially at small
size of cells, and the bump reappeared. To explain all these
changes systematically, mathematical modeling has been used.

By modeling the changes in the cell-size distribution, we can
extract detailed information regarding recruitment, size-depend-
ent growth/shrinkage, size fluctuation, and death of adipose cells.

Figure 4 shows how mathematical models described changes in
the adipose cell-size distributions under different energy balance
conditions (see Table 1 for a detailed description of the model and
parameters). Details for each biological process that we
considered follow:

Recruitment. To describe the change of total cell number
under weight gain and loss conditions, it is a sufficient assumption
that adipose tissues exhibit a net increase in cell number only
during positive energy balance, but not during negative energy
balance. The adipose cell-size probability distribution data by
itself cannot distinguish between a combination of recruitment
and apoptosis, and the net effect of these processes, without
additional immunohistochemistry or staining showing the
frequency of DNA replication and/or apoptosis. Thus, modeling
the temporal changes with both processes included independently
leads to unidentifiable model parameters, and therefore, in the
absence of data fixing the rate of one or the other process, it is
necessary to restrict models to only the net change in cell number.
To provide more storage for excess energy under a high energy
diet, adipose tissues use the two available mechanisms of
hyperplasia and hypertrophy. We have found that hyperplasia
strongly depended on genetics as well as diet, while hypertrophy
depended more on diet.

Growth/shrinkage. The growth rate of adipose cells depends
on cell size. Under small positive energy balance, the cell-diameter
change occurs faster at small cell size (μm), while under
large positive energy balance, the cell-diameter change becomes
constant independent of cell size. The latter observation suggests
that the cell growth rate is determined by surface area. Adipose

![Figure 3. Changes of adipose cell-size distributions under weight gain and loss conditions. C56BL/6 mice were fed with a high-fat diet for 7 weeks,
then with a regular diet for following 12 weeks. Cell-size distributions in epididymal fat depots were measured from different mice at initial time
(3 mo old; black), after 7-week high-fat diet (red) and after 7-week high-fat + 12-week regular diets (blue). Mean ± SEM (n = 6). Note that absolute
frequencies of cell sizes were obtained from their relative frequencies using epididymal fat mass measured.](https://www.landesbioscience.com/Adipocyte/83)
Figure 4. Mathematical models describing cellularity dynamics. Changes of adipose cell-size distribution under various conditions were explained with a general model including recruitment of new adipose cells, growth/shrinkage, and size fluctuation of adipose cells. Detailed explanation of the model and values of model parameters are summarized in Table 1. We simulated four diet conditions: (A) small and (B) large positive energy balances; and (C) small and (D) large negative energy balances. For each condition, left panels show growth rates of cell diameter depending on cell size. Note that negative growth represents cell shrinkage. Here the net growth rates were determined by the balance between lipogenesis (red; increasing cell size) and lipolysis (blue; decreasing cell size). Right panels display 4-week evolutions of cell-size distribution starting from the same initial size distribution (blue) for each condition. Shaded region (gray) below 25 μm is excluded in the simulation since cells below the size have not been systematically measured in experiment. Here the size frequency is normalized as a unity for the initial cell-size distribution.
cell-size changes by two processes: lipogenesis and lipolysis. A simple explanation of the size-dependent growth/shrinkage rate may be that the net growth rate is determined by the balance between lipogenesis and lipolysis. In each process, adipose cells increase/decrease their size in a sigmoidal manner depending on their size. It indicates that large cells above a certain critical size change their diameter proportionally to cell surface area, while small cells change less than the rate expected from cell surface area. This may be due to the fact that the cytosolic volume of the adipose cell becomes increasingly like a thin covering of the central lipid droplet at larger sizes, and therefore leads to lipolysis/ lipogenesis proportional to the surface area of the cell. Note that the critical sizes for lipogenesis and lipolysis are not coincident, and depend on energy balance (Table 1). For positive energy balance, the critical cell size for lipogenesis is smaller than the one for lipolysis, and this relationship is the opposite of that observed during negative energy balance. Then, depending on the relative contribution of lipogenesis and lipolysis, the growth or shrinkage rate of adipose cells showed various forms (Fig. 4).

Size fluctuations. Adipose cells show lipid turnover. Adipose cells release/uptake lipids to/from neighboring cells. This lipid turnover leads to size fluctuation of adipose cells. Modeling shows that this turnover plays an important role in the size of newly recruited small cells. When these cells get larger by random size fluctuations and reach a threshold size, they start to grow at a higher rate. It is this mechanism that is correlated with the bimodality of the adipose cell-size probability distribution. Under a high energy diet, the size fluctuations increase, and provide more chance for the newly recruited small adipose cells to reach the threshold size.

Death. Under a weight loss condition, we have observed that the total number of adipose cells decreases. Two possible explanations are shrinkage of adipose cells below our size-measurement window and death of cells. Bayesian model comparison, quantifying probabilities of different models for explaining the given data, has revealed that the former is more plausible to fit the change of cell-size distribution under the negative energy balance. On the other hand, under a prolonged weight gain condition, we have also observed that total number of adipose cells in epididymal fat decreased, and mathematical modeling revealed that large cells are removed by cell death. If cell death occurred under both weight gain and loss, the former death may be a passive failure for storing energy, while the latter death may be an active process for removing unnecessary energy-storage space.

Table 1. Model parameters

| Parameter | Unit | Description | Small positive energy balance | Large positive energy balance | Small negative energy balance | Large negative energy balance |
|-----------|------|-------------|-------------------------------|-----------------------------|-----------------------------|------------------------------|
| B         | %/week* | recruitment rate | 7                             | 49                          | 0                           | 0                            |
| \(v_{r,\text{max}}\) | \(\mu m/week\) | maximal growth rate | 5.1                          | 9.2                         | 5.0                         | 5.0                          |
| \(\eta_+\) | \(\mu m\) | characteristic size of growth | 30                           | 30                          | 60                          | 60                           |
| \(v_{-\text{max}}\) | \(\mu m/week\) | maximal shrinkage rate | 5.0                          | 5.0                         | 5.1                         | 9.2                          |
| \(\eta_-\) | \(\mu m\) | characteristic size of shrinkage | 60                           | 60                          | 30                          | 30                           |
| D         | \(\mu m^2/week\) | fluctuation rate | 7.4                          | 14.8                        | 7.4                         | 14.8                         |

The mathematical model, describing changes of adipose cell-size frequency \(n(s,t)\) at size \(s\) with time \(t\), is \(\partial n = b(s - s_0) - \partial [n(s)] + D \partial^2 n\). The first term on the right hand side describes recruitment of new adipose cells at the minimal size \(s_0\) with birth rate \(b\). The Kronecker-delta function \(\delta(s - s_0)\), therefore, is 1 only at the minimal size \(s = s_0\), otherwise \(0\). The second term represents growth/shrinkage rates depending on cell size. In particular, we distinguish two processes affecting cell size positively (through lipogenesis) and negatively (lipolysis): \(v(s) = v_+(s) - v_-(s)\), where each component is a sigmoidal function for size \(s\), \(v_\pm = v_{r,\text{max}}\tan h(s/\eta_\pm)\). Finally, the third term corresponds to size fluctuation with fluctuation rate \(D\). *Number of recruiting cells per week is represented as percentile of initial total cell number.

Adipose Cell Turnover

All observations of adipose cells show that adipose cells have an upper size limit. In particular, adipose cells cannot keep increasing their size under positive energy balance. In obesity, cell death at large adipose cells has also been suggested as due to macrophage infiltration and the fragility of enlarged adipose cells. Our mathematical modeling has found that large adipose cells undergo apoptosis or necrosis under prolonged weight-gain conditions. In addition to a failure in storing more energy in obesity, large adipose cells may undergo apoptosis for cell turnover under normal conditions. Spalding et al. have reported that adipose cells are renewed with 10 y lifespan in humans. Therefore, cell turnover may result from the following sequences of events: recruitment of new cells, their growth and death of large, and possibly old, cells. A basic question that may be experimentally addressable is the possibility of a correlation between adipose cell age and size. Our longitudinal study using biopsies of subcutaneous fat tissue from rats has also found oscillation of adipose cell-size distribution with 55 d period (Fig. 5). Unlike the long-term changes of size distributions in adult animals under fixed energy balance (Fig. 3), more dynamic models that consider time-dependent parameters are required to describe dynamic adipose cell-size distributions for the short-term oscillation, developmental period and large alternations of energy balance. One interesting example is the cyclical weight gain and loss of hibernators. Our results show that TZD treatment leads to more adipocytes and greater energy uptake by intermediate-sized adipocytes, in the inguinal fat pad of the Zucker fatty rat. We have quantitatively shown that treatment-induced hyperplasia is more or less complete within the first eight days of treatment, with subsequent hyperplasia at a much slower rate. We have also found that an increase in hypertrophy induced by treatment occurs mainly in...
intermediate-sized adipocytes. This hypertrophy may be related to the greater glucose utilization induced by TZD treatment, which in turn may be linked to increased insulin sensitivity in adipocytes. A similar size range for hypertrophy was found in reference 59, suggesting that the size range for hypertrophy is independent of the stimulus for generating larger adipocytes. On the other hand, the availability of additional adipocytes in a size range capable of additional energy storage due to treatment may itself alleviate hyperglycemia by enabling liponeogenesis. Data in the work of MacKellar et al. shows that the insulin sensitizing effects of TZDs appear by day 2 of treatment but there is a decrease in plasma glucose area-under-the-curve (AUC) between day 6 and day 10 without a concurrent additional drop in insulin AUC. This suggests that the availability of additional energy storage in the form of adipocyte recruitment by day 8 leads to glucose removal from circulation by lipogenesis either in the liver or in the adipose tissue. This may support the hypotheses of de Souza et al.

**Perspective**

We have focused in this review on the dynamic characteristics of adipose tissue that can be elucidated with the combination of precise adipose cell-size probability distributions and mathematical modeling. Even without taking the detailed physiological status of the animals into account, mathematical modeling has elucidated characteristics of adipose tissue cellularity that impact energy storage and availability.

For example, adverse metabolic conditions such as insulin resistance may result from the less responsive behavior of large adipose cells rather than their large size. Large adipose cells are inefficient for energy storage and release: According to our mathematical models, absolute lipolysis per unit mass of adipose tissue is lowered if the proportion of large cells is increased because adipose cell-diameter change is independent of size, implying lipid absorption/release proportional to cell surface area. In addition, prolonged weight gain ultimately induces the death of large cells. Therefore, hypertrophy by itself is inadequate for storing excess energy, and leads to hyperplasia. However, lipodystrophy/lipotoxicity induced by a dysfunction in lipid storage by adipose cell hypertrophy induces inflammation (due to reactive oxygen species generation, for example) affecting small adipose cells as well as large cells. Thus, insights from mathematical modeling can provide an integrative view of adipose cellularity in metabolic syndromes. As another example, the impact of TZD administration appears to decouple the insulin-sensitizing effects and the recruitment of new adipocytes. This conclusion, reached by mathematical modeling of cell-size distribution changes under TZD administration, has been confirmed by molecular studies.

**Figure 5.** Oscillation of adipose cell-size distribution. Adipose cell-size distributions were measured in a Zucker fa/fa rat (4 weeks old) over a period of 151 d, using micro-biopsies to obtain subcutaneous (inguinal) fat tissue from the animal. The biopsies were done on days 0, 2, 6, 9, 13, 23, 33, 57, 69, 86, 98, 134, 141 and 150. Their cell-size distributions could be consecutively categorized into five stages (S1 to S5) based on the Bayesian analysis of data. Those stages appear periodically with an interval of ~55 d.
Mathematical modeling also sheds light on the origin of bimodality. The origin of the nadir observed between the large number of adipose cells at small size and the other modal number at medium size is the size-dependent growth of adipose cells, coupled with size fluctuations associated with lipid turnover. Thus, newly recruited cells accumulate at small sizes (< 30 μm) unless size fluctuations move them to a size at which they can store lipids efficiently, leading to growth to larger sizes. Hence, the bimodality may represent two distinct populations of adipose cells.

Size-dependent features of adipose cell growth/shrinkage and death have not been explored in experiments. The changes of adipose cell size through lipogenesis and lipolysis will be linked to the lipid-droplet configurations. Small cells in WAT have multiple (multilocular) small lipid droplets, while large cells have multilocular lipid droplets. It is of interest that adipose cells in brown adipose tissue, playing a role for energy dissipation, have multilocular lipid droplets. This physical configuration of droplets may affect lipid absorption and release due to the surface-to-volume ratio of entire droplets in cells. Furthermore, several molecules such as fat-specific protein of 27 kDa (FSP27) and caveolin, involved in the lipid droplet formation, have been identified. Therefore, recent intensive studies regarding lipid droplets may shed light on the microscopic details of size-dependent adipose cell growth and shrinkage.

Further progress in relating the mechanistic changes in the cellulosity of adipose tissue and the metabolic state of the animal will require cell-size distribution measurements along with measurements of insulin, leptin, adipokines, cytokines and circulating metabolites.

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