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Review

Transforming growth factor beta superfamily regulation of adipose tissue biology in obesity

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ABSTRACT

Accumulation of dysfunctional white adipose tissues increases risks for cardiometabolic diseases in obesity. In addition to white, brown or brite adipose tissues are also present in adult humans and increasing their amount may be protective. Therefore, understanding factors regulating the amount and function of each adipose depot is crucial for developing therapeutic targets for obesity and its associated metabolic diseases. The transforming growth factor beta (TGFβ) superfamily, which consists of TGFβ, BMPs, GDFs, and activins, controls multiple aspects of adipose biology. This review focuses on the recent development in understanding the role of TGFβ superfamily in the regulation of white, brite and brown adipocyte differentiation, adipose tissue fibrosis, and adipocyte metabolic and endocrine functions. TGFβ family and their antagonists are produced locally within adipose tissues and their expression levels are altered in obesity. We also discuss their potential contribution to adipose tissue dysfunction in obesity.

1. Introduction

1.1. Accumulation of dysfunctional adipose tissue in obesity increases risk for cardiometabolic diseases

Adipose tissues are the most plastic organs and can expand or contract depending on metabolic status. Obesity, defined as accumulation of excess white adipose tissue (WAT), develops when surplus in energy balance continues and obese subjects are at higher risk of developing multiple cardiometabolic diseases including insulin resistance, type 2 diabetes, cardiovascular diseases, and several types of cancer [50]. Adipose tissues play critical roles in systemic energy homeostasis and dysfunctions in adipose tissues, which are characterized by hypertrophied adipocytes, fibrosis, hypoxia, and high inflammation, are thought to contribute to the development of metabolic diseases in obesity [15]. Deficiency of adipose tissues (lipodystrophy) is also associated with systemic metabolic complications, further emphasizing the importance of maintenance of adipose tissue for systemic health.

1.2. Different types of adipose tissues are present at multiple locations

Different shades and colors of adipose tissues, white, brite, and brown, are present at multiple locations throughout an organism. In humans, WATs are classified largely into two categories, visceral and subcutaneous depots, and subcutaneous depots are further subdivided into the upper-body (abdominal) and lower-body (gluteofemoral) fat. Adipose tissue distribution pattern varies among individuals and central obesity, fat accumulation both in the visceral and abdominal subcutaneous depots, is known to be more detrimental while accumulation in the lower-body confers protection against metabolic complications [50]. Brown adipose tissue (BAT) or inducible brown adipocytes (brite, also called as beige) in WAT are also present in adult humans and their amount is reported to be reduced in obesity [95]. Brown and brite adipocytes have the unique capacity to burn energy by activating adaptive thermogenesis due to high mitochondrial density as well as expression of uncoupling protein-1 (UCP1) and fatty acid oxidation genes. Due to the high capacity to burn energy, increasing the amount and activity of brown and brite adipose tissues are thought to be beneficial for obesity and its related metabolic diseases. At least in mouse models, the beneficial effects of enhancing the amount and activity of brown and brite adipose tissues through cold exposure or beta-adrenergic receptor (β-AR) agonist treatment have been demonstrated [72,88]. In vivo cold exposure or treatment with adrenergic agonists also induces britening of subcutaneous adipose tissues in humans [16,44], implicating the physiological relevance of britening in humans. The potential of increasing the amount and activity of brown and brite adipocytes to dissipate excess energy to target obesity and its related diseases in humans is under investigation.

1.3. Adipose progenitors reside in stromal fraction in each depot

Most of adipose progenitors, precursors for adipocytes, are thought

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to reside within stromal compartment of each adipose depot and replenished through replication and recruitment, although they can be recruited from circulation. In vivo lineage tracing studies in mice suggest that white, brown, and brite adipocytes are derived from distinct progenitors (reviewed in [68]). Earlier studies indicated that brown and beige (brite) adipocytes are derived from Myf5+ myogenic progenitors while white adipocytes are derived from Myf5- cells. However, later studies have shown that Myf5+ cells can also label subpopulation of white adipocytes. The precise identity of each adipose progenitor is not completely defined and even within a depot, different adipose progenitors with variable proliferation and differentiation capacities may be present [68]. Further, adipose progenitors contain characteristics of MSCs with multi-lineage potential and their differentiation into 'a kind of adipocytes' is influenced by multiple hormones, cytokines, growth factors, and other factors that reside within the local environment of adipose tissues at a given time.

Adipose progenitors can be isolated from stromal vascular fraction using different surface markers and are thought to be CD31-/CD45-/CD29+/CD34+/CD90+/CD105+ in humans [3], similar to bone marrow mesenchymal stem cells (BM-MSCs) [20]. There is no complete consensus on the cell surface antigen profile that will precisely define human adipose progenitors and different combinations of markers are used among different studies. In vitro studies using isolated adipose stromal cells (ASCs) and adipose progenitors from different human and mouse adipose depots suggest that there are also depot-dependent heterogeneities in adipogenic capacity and proliferation rates [49,55]. More studies are needed to define and characterize adipose progenitors in different adipose depots and whether their relative abundances are affected by physiological status including adiposity.

1.4. Limited expansion capacity of adipose tissues leads to ectopic fat deposition in obesity

Adipocytes continuously remodel throughout a life-span and therefore, recruitment of adipose progenitors and their differentiation into adipocytes are crucial for the maintenance of adipose tissues. Differentiation of adipose progenitors into mature adipocytes, adipogenesis, is a multi-stage process involving cell fate determination, clonal expansion, and terminal differentiation and regulated by numerous autocrine, paracrine and endocrine factors [49]. Complex array of adipogenic transcription factors including C/EBPα, C/EBPβ, and PPARγ, which exhibit temporal expression pattern during adipogenesis, control differentiation and PPARγ is regarded as the master regulator of adipogenesis [60]. Most of endocrine and autocrine/paracrine factors regulate adipogenesis by affecting the expression level or transcriptional activity of PPARγ.

Adipocytes comprise most of the volume of adipose tissues and adipose tissues expand through increasing the size (hypertrophy) or numbers (hyperplasia) of adipocytes. Adipogenic capacity of ASCs isolated from human adipose tissues is reported to be reduced in obesity. Limited expandability through hyperplasia especially in subcutaneous depots in hypertrophic obesity is thought to cause ectopic fat deposition, a well-known risk factor for insulin resistance and other cardiometabolic diseases [32]. Therefore, continuous supply of precursor cells and their differentiation into new adipocytes are crucial for the maintenance of systemic health as well as adipose tissues. Reduced numbers of adipose progenitors and high expression levels of proinflammatory cytokines have been suggested to contribute to the lower adipogenic capacity in the hypertrophic obesity [32]. In addition, alterations in TGFβ signaling may also contribute to the reduced adipogenic capacity of ASCs in obesity, as discussed below.

1.5. Cell culture models used for the studies of adipogenesis

Culture models that are most commonly used for studies of adipogenesis are briefly discussed. We refer to the previous reviews [49,60] for more details.

1.5.1. 3T3-L1 and 3T3-F422A cells

3T3-L1 and 3T3-F422A cells are mouse cell lines that are selected clones of fibroblast stocks derived from Swiss 3T3 mouse embryos based on their high adipogenic potential. 3T3-F422A cells have higher adipogenic potential than 3T3-L1 and thought to be more committed to adipogenic lineage. Both cell lines can be expanded extensively without losing adipogenic capacity and most widely used for studies of adipogenesis. They have been invaluable for identification of adipogenic transcriptional factors and factors that regulate adipogenesis [60].

1.5.2. C3H10T1/2 cells

C3H10T1/2 (10T1/2) cells, derived from C3H mouse embryos, contain characteristics of MSCs and frequently used for studies of adipogenic lineage commitment to both white and brown adipocytes. A33 clone of 10T1/2, selected after treatment with 5′-azacytidine, an inhibitor of DNA methylation, exhibits higher adipogenic capacity than the parental cells [8].

1.5.3. Mesenchymal stem cells (MSCs)

Multipotent mesenchymal stem cells have been identified in many adult tissues, most well-known for bone marrow but also in adipose tissues. MSCs are isolated based on their adherence to culture plates in the standard culture condition and known to be CD45-/CD14-/CD31-/CD73+/CD90+/CD105+ [20]. In vitro cell culture conditions influence immunophenotypes of MSCs and initially they are thought to be CD34- but later freshly isolated MSCs are known to be CD34+ [54]. MSCs contain multi-lineage potential and therefore, are useful for studies of adipogenic lineage commitment.

1.5.4. Adipose tissue stromal cells (ASCs)

Although cell culture models have been invaluable, potential sex- or depot-dependent differences in adipogenesis cannot be addressed in cell lines. Further, there may also be species-dependent differences in adipogenic programs. Therefore, use of ASCs derived from human adipose tissues has been increasing. Isolated stromal vascular fraction of adipose tissues contain multiple cell types including adipose progenitors, preadipocytes (presumably more committed to the adipogenic lineage), endothelial cells, and various immune cells. Once plated and cultured several times, stromal cells lose heterogeneities and acquire MSC characteristics [3]. It is also possible to select relatively homogeneous cell populations based on immunophenotypes. ASCs are also called as adipose tissue stem cells, adipose-derived adult stem cells, adipose progenitors, or preadipocytes.

2. TGFβ superfamily proteins

The transforming growth factor beta (TGFβ) superfamily consists of more than 33 members and includes TGFβ1, 2, and 3, bone morphogenetic proteins (BMPs), growth differentiation factors (GDFs), activins and nodal-related proteins. TGFβ superfamily members control diverse cellular processes including cell growth, cell fate specification, and differentiation [11]. Not surprisingly, many members of TGFβ superfamily exert pleiotropic actions on adipose tissue biology, most well-known for their effects on adipogenesis.

TGFβ1, 2, and 3 are expressed as precursors with an N-terminal signal peptide followed by a prodomain, furin protease cleavage site, and C-terminal mature peptide sequence [11]. The mature peptide is converted into a disulfide-linked dimer and secreted from cells in a large latent complex (LLC) consisting of TGFβ dimer, its dimeric propeptide referred as latency-associated peptide (LAP), and a latent TGFβ-binding protein (LTBP) [65]. The LLC remains in the extracellular matrix (ECM) through binding to fibronectin fibers and fibrillin microfibrils until it is further processed to release active TGFβ, which then binds to membrane receptors and initiates signal transduction.