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Metabolic Flexibility in Fat Tissue during ATP Surplus and Fibroblast Trans Differentiation.

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Abstract: This narrative review examines the involvement of obesity and inflammation in remodeling fibroblasts into adipocytes. It outlines the process of adipogenesis, and the transcription factors (e.g., PPARγ, C/EBPα) involved in the differentiation of fibroblasts into adipocytes. The role of adipose tissues and adipokines in regulating metabolism, insulin sensitivity, and inflammation is discussed. The therapeutic potential of targeting adipokines and fibroblasts in various diseases, such as diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease, and infertility is highlighted. This review focuses on the therapeutic potential of the fibroblast-to-adipocyte conversion, specifically highlighting its differentiation into energy-expending Brown or Beige Adipocytes (browning). We synthesize current knowledge on the molecular pathways (e.g., PPARγ, C/EBPα) and extracellular signals, including adipokines, that drive this beneficial transdifferentiation.

Keywords: Fibroblast, Adipogenesis, Obesity, Browning, Brown Adipocyte, UCP1, Cellular Plasticity

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Introduction

Obesity is a major risk factor for type 2 diabetes and heart disease. It can result from a combination of genetic, biological, and environmental influences, such as a high-calorie diet, lack of physical activity, alcohol consumption, family background, and smoking [1, 2]. Obesity involves abnormal fat buildup, marked by both the enlargement (hypertrophy) and increase in number (hyperplasia) of fat cells [1]. In obese adipose tissue, macrophages infiltrate the tissue and undergo functional polarization. They switch from the anti-inflammatory M2 type to the pro-inflammatory M1 type. This change is triggered in part by the secretion of adipokines [3].

Adipocytes are derived from Mesenchymal Stem Cells (MSCs) which are initially converted to lipoblasts, then preadipocytes, and ultimately mature adipocytes [4]. Several studies have reported that fibroblasts retain considerable plasticity and have the capability to transdifferentiate into other cell types including adipocytes if provided with adequate nutritional medium and transcription factors [4-6]. This article aims to explore the diverse molecular, hormonal, and pharmacological factors that can induce beneficial adipogenesis in fibroblast cell lines, with a specific emphasis on directing this differentiation toward the highly metabolically active Brown or Beige Adipocyte phenotypes. By identifying these critical upstream signals and transcription factors, we seek to uncover novel pharmacological targets for promoting energy expenditure and

expand understanding of obesity pathophysiology. The challenge of uncontrolled plasticity (Figure 1) highlights the need for a therapeutic solution, which is proposed by the beneficial fibroblast browning pathway (Figure 2).

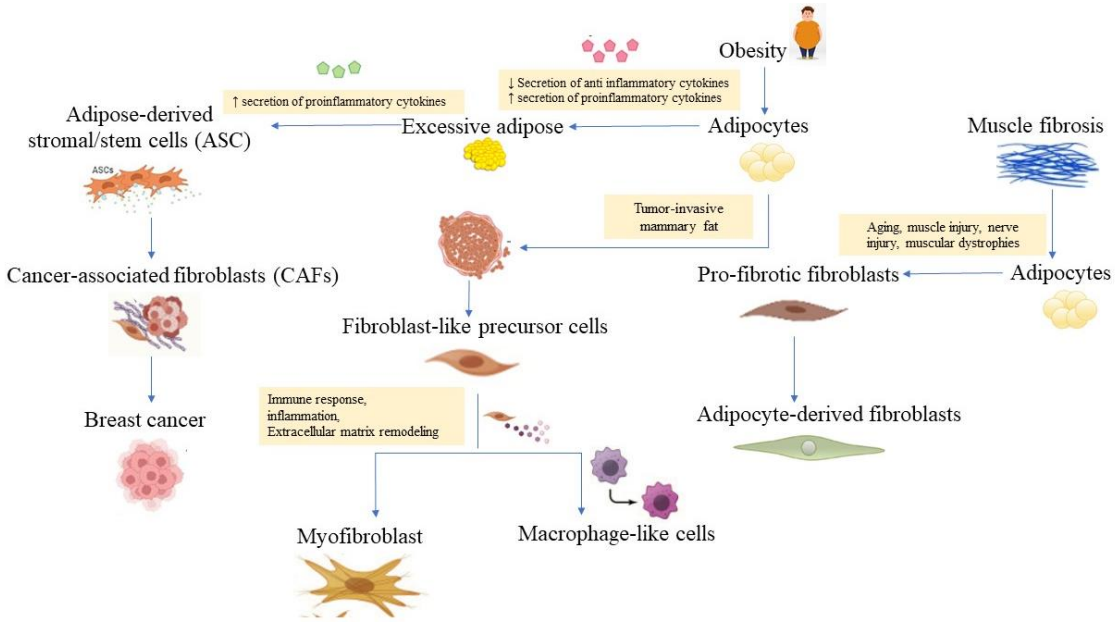

Figure 1: Pathological Adipocyte Plasticity (Detrimental Reverse Conversion).
This figure summarizes the negative cell fate conversions that occur in obesity. The transition of adipocytes or ASCs to pro-fibrotic fibroblasts, myofibroblasts, and Cancer-Associated Fibroblasts (CAFs) contributes to organ fibrosis, chronic inflammation, and cancer progression. This detrimental plasticity highlights the need for therapeutic strategies that actively steer fibroblasts toward a beneficial, energy-expending fate.

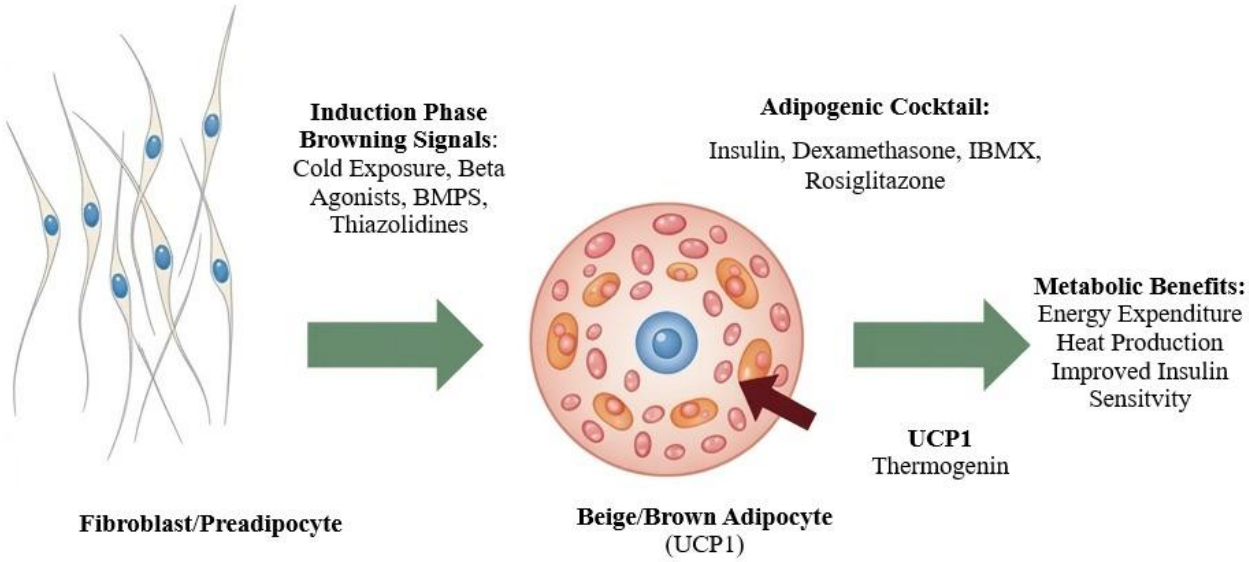

Figure 2: **Therapeutic Fibroblast Browning for Metabolic Health.**
The figure illustrates the process of browning, where Fibroblasts or Adipose-derived Stromal/Stem Cells (ASCs) are induced to differentiate into metabolically active Beige or Brown Adipocytes. This conversion is achieved through specific induction signals (e.g., cold exposure, beta-agonists, BMPs, Thiazolidinediones) combined with an adipogenic cocktail (Insulin, IBMX, Dexamethasone, etc.). The resulting Brown/Beige Adipocytes are characterized by the expression of Uncoupling Protein 1 (UCP1), which promotes thermogenesis and energy expenditure. This process may offer significant therapeutic potential for treating obesity, Type 2 Diabetes, and Metabolic Syndrome by improving insulin sensitivity and reducing excess fat burden.

Adipocyte Morphology

The process of adipogenesis, essential for the maturation and functionality of adipocytes, begins with the differentiation of preadipocytes. These preadipocytes then undergo further differentiation to become fully functional adipocytes, capable of storing and releasing energy as triglycerides [6]. Adipose tissue comprises two distinct types: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT mainly stores energy, while BAT is designed to generate heat through the uncoupling of mitochondrial respiration [7].

WAT is classified into two types: subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). SAT is commonly located in the gluteofemoral, back, and anterior abdominal regions. VAT is concentrated around internal organs though mostly present around those in the abdominal cavity and is further subdivided into mesenteric, omental, perirenal, and peritoneal depots. VAT contains fewer preadipocytes and larger adipocytes as compared to SAT which tends to contain more small adipocytes [8].

Molecular Mechanisms for Directing Fibroblast-to-Brown/Beige Adipogenesis

Multiple inducers have been tested to demonstrate this phenomenon. [9]. In 2021 a small molecule STK287794 was reported to upregulate C/EBPα and PPARγ in human dermal fibroblasts converting them into BAT under defined cultural conditions [10]. Another study reported PRDM16 gene transduction in the presence of retinoic acid as a medium for the conversion of dermal fibroblasts into brown adipocytes [11].

Other regulators include Krüppel-like factors (KLFs) which promote adipogenic expression while suppressing alternative lineage programs. Skeletal muscles also contain fibroblasts that have been reported to undergo adipogenesis when stimulated with fatty acids or adipocyte-inducing medium, mimicking diseased states such as obesity and type-2 diabetes. This conversion has been reported as one of the possible causes of increased intramuscular adipocytes in these condition [12].

Inhibition of 3-Mercaptopyruvate sulfur transferase in dermal fibroblasts has been reported to induce adipogenesis and conversion into WAT under acidic, oxidative conditions [13]. In contrast, exposure of adipose-derived stromal/stem cells from obese individuals to tumor-derived signals increases their likelihood of differentiating into cancer-associated fibroblasts. These cells exhibit elevated expression of CAF markers and promote extracellular matrix remodeling and inflammation [14, 15, 16, 17].

Commitment to Adipocyte Lineage

The first crucial step of adipocyte commitment can be influenced by the hypomethylation of specific genes [6, 18, 19]. This is followed by differentiation where preadipocytes undergo mitotic clonal expansion in response to various hormonal stimuli [20-22]. Cells then decrease CDK inhibitors such as p21, enabling cell-cycle re-entry. Early C/EBP β/δ activation drives PPAR-γ and C/EBP α, completing adipocyte maturation. PPAR-γ turns on fatty-acid genes (Fasn, Acc1, Srebp1), and β-adrenergic/AMPK signaling promotes lipolysis and thermogenesis. These factors are also crucial for brown adipocyte differentiation and may be a potential future target for anti-obesity strategy. As targeting MCE before differentiation allows a larger pool of preadipocytes ready for brown adipogenic switch. [9, 20, 23-26].

Maturation into Adipocytes

The commitment and differentiation of preadipocytes are tightly regulated by protein regulators, epigenetic modifications, and microRNAs. The extracellular matrix plays a critical role, with components such as fibronectin maintaining preadipocytes in an undifferentiated state. As differentiation progresses, signaling molecules including metabolic hormones (e.g., adiponectin and leptin) and angiogenic factors (e.g., VEGF) support healthy adipose tissue development.

Conversely, proinflammatory adipokines such as CXCL8, IL-6, and TNF-α may impair adipocyte maturation and promote dysfunctional adipose remodeling [27-30]. In vivo lineage tracing studies in rodents have shown that WAT expansion during obesity occurs in a depot- and sex-dependent manner, highlighting the influence of sex hormones on adipocyte hyperplasia and hypertrophy [31].

Conclusion

The ability to induce brown or beige adipogenesis from local fibroblasts offers a promising strategy to increase energy expenditure via uncoupling protein 1 (UCP1) mediated thermogenesis while safely sequestering excess lipids. Understanding the precise signals that determine the fibroblast to brown adipocyte fate, particularly those involving adipokines and epigenetic regulation, is critical. This knowledge may guide the development of new treatments for obesity and related metabolic illnesses by harnessing the body's intrinsic potential for 'fat browning'.

Ethics Approval and Consent To Participate

Not applicable.

Human and Animal Rights

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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