Differentiation 87 (2014) 183–192

Contents lists available at ScienceDirect

Differentiation

journal homepage: www.elsevier.com/locate/diff

Review

Adipocyte transdifferentiation and its molecular targets

Sujith Rajan [a,b], Abhishek Gupta [a], Muheeb Beg [a], Kripa Shankar [a], Ankita Srivastava [a,b], Salil Varshney [a], Durgesh Kumar [a,b], Anil Nilkanth Gaikwad [a,b,*]

[a] Division of Pharmacology, CSIR-Central Drug Research Institute, Lucknow, 226031 UP, India
[b] Academy of Scientific and Innovative Research, CSIR-CDRI, India

ARTICLE INFO

Article history:
Received 6 February 2014
Received in revised form
2 July 2014
Accepted 24 July 2014
Available online 15 August 2014

Keywords:
Transdifferentiation
Brown adipocyte
Paucilocular adipocyte
Thermogenesis
PRDM16
PGC1α

ABSTRACT

According to the World Health Organization obesity is defined as the excessive accumulation of fat, which increases risk of other metabolic disorders such as insulin resistance, dyslipidemia, hypertension, cardiovascular diseases, etc. There are two types of adipose tissue, white and brown adipose tissue (BAT) and the latter has recently gathered interest of the scientific community. Discovery of BAT has opened avenues for a new therapeutic strategy for the treatment of obesity and related metabolic syndrome. BAT utilizes accumulated fatty acids for energy expenditure; hence it is seen as one of the possible alternates to the current treatment. Moreover, browning of white adipocyte on exposure to cold, as well as with some of the pharmacological agents presents exciting outcomes and indicates the feasibility of transdifferentiation. A better understanding of molecular pathways and differentiation factors, those that play a key role in transdifferentiation are of extreme importance in designing novel strategies for the treatment of obesity and associated metabolic disorders.

Contents

1. Introduction

Obesity has reached a pandemic level and is no longer a disease of developed nations. It is characterized by an increase in the mass of adipose tissue (Smorlesi et al., 2012; Tseng et al., 2010). Obesity results from excess energy intake than actual expenditure. Excess energy is stored in the adipocyte in the form of triglycerides (Cinti, 2006). Apart from lipid storage, adipose tissue is a major endocrine organ secreting more than 33 adipokines such as leptin, adipsin, adiponectin, Acrp30, etc. (Van deVoorde et al., 2013). Obesity is the stem of other metabolic disorders such as insulin resistance, dyslipidemia, fatty liver disease, Type 2 diabetes mellitus, hypertension and cardiovascular diseases, etc. All these

* Correspondence to: BS 10/1, Sector 10, CSIR-Central Drug Research Institute, Jankipuram Extension, Lucknow 226031, Uttar Pradesh, India.
Tel.: +91 522 2771940x4876; fax: +91 522 2771941.
E-mail address: anil_gaikwad@cdri.res.in (A.N. Gaikwad).

http://dx.doi.org/10.1016/j.diff.2014.07.002
Join the International Society for Differentiation (www.isdifferentiation.org)
0301-4681/

disorders are often associated with metabolic disturbances, commonly recognized as metabolic syndrome (Ray, 2013). Recent studies have given good insight into the physiology of adipose tissue and different fat pads located in the human body. There are two types of adipose tissue white adipose tissue (WAT) and brown adipose tissue (BAT) (Cinti, 2012; Giralt and Villarroya, 2013; Madsen et al., 2010). Former specializes in the storage of energy in periods of positive energy balance and mobilizes the stored energy during starvation. Whereas, the brown adipocytes with the help of uncoupling protein-1 (UCP1) use stored triglycerides to produce heat in a process called thermogenesis (Nicholls and Rial, 1999). The balance between WAT and BAT in the body is essential to maintain energy homoeostasis. Accumulation of excess white adipose tissue, especially in the visceral compartment leads to metabolic and cardiovascular complication (Nicholls and Rial, 1999). Obesity, over a prolonged period leads to the development of insulin resistance and eventually to the type 2 diabetes mellitus. The association between obesity and insulin resistance is likely a cause-and-effect relationship. Numerous animal and human studies have indicated a close correlation between weight loss/weight gains with decrease/increase in the insulin resistance (Cinti, 2012). As weight gain is largely due to increased WAT, insulin resistance therefore can directly be correlated with the gain in adipose tissue mass (Ray, 2013). The secretory function of WAT has been recognized as the link for this correlation (Giralt and Villarroya, 2013). WAT acts as a sink of deleterious fatty acids and excess of which leads to lipotoxicity (Ray, 2013). In the context of the above mentioned complications, the best strategy to treat obesity is to find a way to utilize the deleterious fatty acids accumulated in WAT without harming other tissues and organs. The idea of recruiting brown adipocytes as a means to utilize the excess fatty acid has fascinated researchers for a long period, since the serendipitous discovery of BAT in adults. In this review, we have focused on recent developments and possibilities to activate or expand brown adipose tissue. We have tried to elucidate the relevance of the browning phenomenon as a therapeutic target for the treatment of obesity and its metabolic complications. We have also reviewed the role of different proteins and transcription factors in differentiation of brown adipocyte as well as their contribution to browning phenomenon.

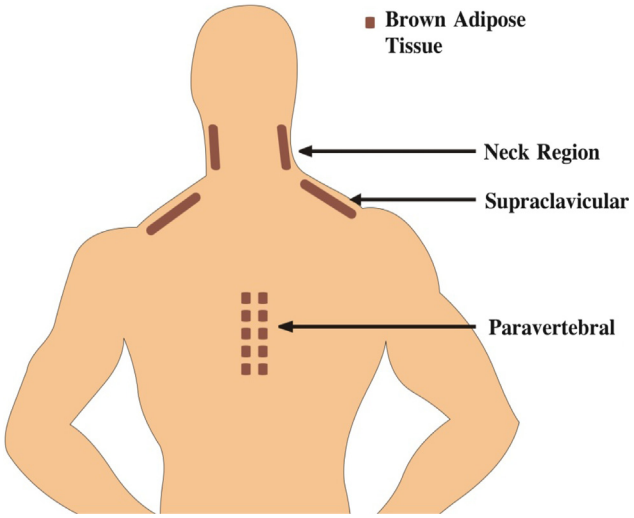

Fig. 1. Location of BAT in normal, healthy human. BAT locations are marked with brown shade and the corresponding region is labelled with an arrow mark. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2. Discovery of brown adipose tissue in adults

Until 1979, brown adipocytes were believed to be absent in adults and were thought to be present only in rodents and newborns (Rothwell and Stock, 1979). The discovery of brown adipocytes was further proved by 18F-Fluorodeoxy glucose positron emission tomography/computed tomography (FDG-PET/CT) (Hadi et al., 2007). De Matteis et al., focused on immunohistochemical analysis of adipose tissue from the neck region of the patients undergoing thyroid surgery and found a clear characteristic of BAT in one third of the subjects (De Matteis et al., 2009). Independent research groups had confirmed the presence of BAT by verifying the level of UCP1 expression in biopsy samples taken from the active glucose uptake tissues (Frontini et al., 2013). Predominantly, BAT is present in cervical, supraclavicular and the paravertebral region in healthy adults (Fig. 1).

Orava et al., investigated a group of five healthy volunteers subjected to both warm and cold temperatures. Cold temperature led to 15 fold increase in FDG uptake in supraclavicular region. when biopsies of corresponding fat tissue were compared with WAT, they found increased expression of UCP1 at gene and protein levels as well as higher expression of other markers of BAT (Orava et al., 2013). The activity of BAT was significantly lower in overweight and obese subjects compared to lean and healthy subjects. BAT measurement in subjects with Body Mass Index (BMI) 25.4–38.7 were between 8 and 146 cm^3 depot, while lean and healthy subjects with BMI 21.3–24.5 showed between 32 and 228 cm^3 (Lidell et al., 2013). BAT is found to be more common in adolescence than in adults. The presence and volume of BAT increase rapidly during puberty and reaches a peak at the age of adolescence (Lidell et al., 2013; Orava et al., 2013). In adults, the presence of BAT is independently associated with a lower likelihood of NAFLD, a well known marker of the metabolic syndrome (Ray, 2013). FDG-PET/CT scan of 2000 subjects by Cypess et al. indicated the presence of BAT in 7% women and 3% men (Cypess et al., 2013;

Table 1
Difference between white and brown adipocytes.

White adipocytes	Brown adipocytes
Develops after birth	Develops at neonatal stage
Increases with age	Decreases with age
Large in size	Small in size
Unilocular lipid droplets	Multilocular lipid droplets
Low iron concentration	High iron concentration
Less mitochondria with thin cristae	More number of mitochondria with dense cristae
Poorly developed capillaries and vasculature in WAT	Highly developed vasculature in BAT
Found in subcutaneous, visceral and epididymal fat pads	Found in neck supraclavicular, cervical, and paravertebral regions
Less β3 adrenergic receptor present	Large number of β3 adrenergic receptor present
Less sensitive to sympathetic nervous system	Highly sensitive to the sympathetic nervous system
Do not express UCP1	High UCP1 expression