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REGULAR ARTICLES

The possible potentiating role of endoplasmic reticulum stress response inhibitors in trans-differentiation of white to brown adipocytes

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Abstract The brown adipose tissue (BAT) is an organ with the specialised function of intracellular fat oxidation; in other words, brown fat points to a potential natural tool by which energy expenditure is being stimulated. Obesity is a serious illness which can lead to many medical complications such as cardiovascular disorders. The BAT production, therefore, could be a promising therapeutic strategy for managing obesity. While different approaches have been examined to generate brown adipocytes from various precursor cells, no study has proposed an efficient procedure for direct trans-differentiation of white to brown adipocytes. Bone morphogenic protein (BMP)-7 is a possible potential agent by which most of the main factors involved in induction of brown adipocytogenesis such as early regulators of brown fat fate, positive regulatory domain containing 16 (PRDM16) and peroxisome proliferator-activated receptor gamma (PPARγ) coactivator-1 alpha (PGC-1α) are stimulated, but the rate of success was not so promising. It has been documented that mature white adipocytes exert endoplasmic reticulum stress response (ESR) and consequently unfolded protein response (UPR) becomes activated for the purpose of ESR recovery since the ESR exceeds the capacity of UPR to overcome the imposed stress, and in turn disables the cell to manage the protein synthesis cascade including those required for BMP-7 induction of brown adipogenesis. This was performed using three main ESR sensors: PKR-like endoplasmic reticulum kinase (PERK), inositol requiring enzyme-1 (IRE-1) and activating transcription factor 6 alpha (ATF-6α) resulting in

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attenuation of protein translation by blocking the activation of transcriptional machinery of UPR genes and the cell behaviour would also be changed towards apoptosis.

It may suggest and propose the hypothesis that pretreatment of the white adipocyte with an ESR inhibitor such as salubrinal by reducing ESR and turning on the protein synthesis machinery required for BMP-7 induction of brown adipogenesis cascade could provide a more efficient and successful method of transdifferentiation procedure of white to brown adipocytes.

Introduction

The prevalence of obesity is increasing worldwide resulting in major health problems such as type 2 diabetes, ischaemic heart disease, stroke and cancer. It is a necessity to find safer medication to treat obese individuals [1] but the pure cure does not currently exist. In all mammals, a multi-depot organ called the adipose organ contains white and brown adipocytes [2]. While white fat cells are specialised in storage of energy in the form of triglycerides, brown adipocytes (BATs), catabolise free fatty acids (FFAs) and consume stored energy as heat [3]. The recent development of new concepts regarding the biology of adipose tissue in mammals had led to the hope for a hot issue highlighting BAT development in adults as a new challenge for treatment of obesity and related diseases. There is evidence in the last few years supporting the concept of an alteration in energy balance by converting white to brown adipose tissue [4].

Bone morphogenic proteins (BMPs), members of transforming growth factor β super-family, are responsible for the control of multiple key steps in embryonic development and play an important role in differentiation [5] and appear to have different roles in adipogenesis [6]. Some studies have proposed that treatment of humans with BMP-7 or its molecular mimetic may recruit and activate brown fat differentiation, leading to an elevation in energy expenditure, and thereby providing a new avenue to combat obesity [7]. Although some studies have accomplished BMP7-induced brown adipocyte differentiation from various cell types such as C3H10T1/2 cells (mesenchymal progenitor/stem cells) or brown preadipocytes with standard adipogenic differentiation cocktail supplemented [7], as the number of the white adipocytes are not altered, the person still predisposes to obesity since it is documented that both increase in the number of cells through adipocyte proliferation (hyperplasia) and increase in adipocyte size (hypertrophy) lead to adipose tissue expansion [8]. The question therefore will be, how the number and triglyceride (TG) accumulation of white adipocytes could be reduced? *In vitro* studies have demonstrated that BMP7 is able to differentiate brown preadipocytes into brown adipocytes. Although the plasticity of adipocytes is well documented, no study has examined BMP7's potential role on direct trans-differentiation of white to brown adipocytes [9]. How could this be explained? It may partly be due to the endoplasmic reticulum stress response (ESR). ESR refers to the cellular condition present

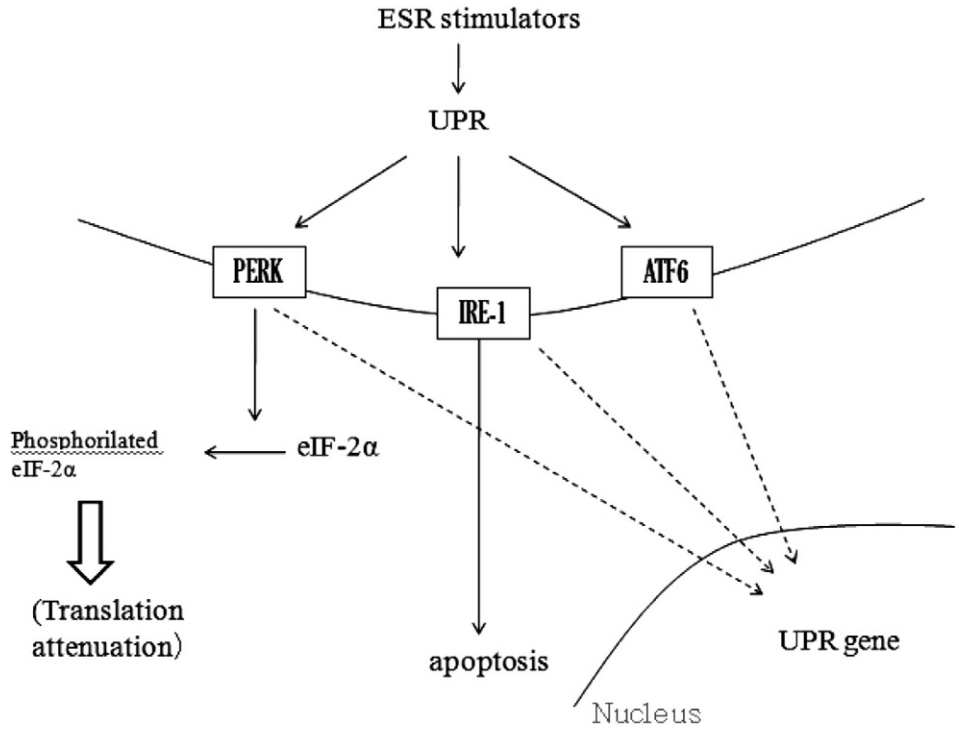

Figure 1 UPR (unfolded protein response) signaling pathway. Endoplasmic stress response (ESR), PKR-like endoplasmic reticulum kinase (PERK), inositol requiring enzyme-1 (IRE-1), activating transcription factor 6 (ATF-6), eukaryotic initiation Factor 2 alpha (eIF-2α).