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Minireview

The potential role of inhibitor of differentiation-3 in human adipose tissue remodeling and metabolic health

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ABSTRACT

Metabolic health in obesity is known to differ among individuals, and the distribution of visceral (VAT) and subcutaneous adipose tissue (SAT) plays an important role in this regard. Adipose tissue expansion is dependent on new blood vessel formation in order to prevent hypoxia and inflammation in the tissue. Regulation of angiogenesis in SAT and VAT in response to diet is therefore crucial for the metabolic outcome in obesity.
Knowledge about the underlying genetic mechanisms determining metabolic health in obesity is very limited. We aimed to review the literature of the *inhibitor of differentiation-3* (*ID3*) gene in relation to adipose tissue and angiogenesis in humans in order to determine whether *ID3* could be involved in the regulation of adipose tissue expansion and metabolic health in human obesity.
We find evidence that *ID3* is involved in regulatory mechanisms in adipose tissue and regulates angiogenesis in many tissues including adipose tissue. We discuss how this might influence obesity and metabolic health in obesity and further discuss some potential mechanisms by which *ID3* might regulate visceral and subcutaneous adipose tissue expansion.
The combined results from the reviewed literature suggest *ID3* to play a potential role in the underlying regulatory mechanisms of metabolic health in human obesity. The literature is still sparse and further studies focusing on human *ID3* in relation to the nature of obesity are warranted.

Contents

Abbreviations: ASC, Adipose-derived stem cells; BAT, Brown adipose tissue; BMI, Body mass index; bHLH, Basic helix–loop–helix; DNA, Deoxyribonucleic acid; DIO, Diet induced obesity; FAS, Fatty acid synthase; FFA, Free fatty acid; GWAS, Genome wide association study; HFD, High-fat diet; ID (ID), Inhibitor of differentiation gene (human protein); Id, Inhibitor of differentiation (rodent gene); ID3L (ID3A), Long isoform of ID3 protein human (rodent); IMT, Intima–media thickness; mRNA, Messenger ribonucleic acid; NPAF, Neuropeptide AF; NPFF, Neuropeptide FF; NPSF, Neuropeptide SF; p21cip1, Cyclin-dependent kinase inhibitor 1; PCG-1α, Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha; PDGF, Platelet-derived growth factor; SAT, Subcutaneous adipose tissue; SNPs, Single nucleotide polymorphisms; SREPB-1c, Sterol Regulatory Elements Binding Protein 1-c; SVF, Stromal vascular fraction; UCP-1, Uncoupling protein 1; VAT, Visceral adipose tissue; VEGFA, Vascular endothelial growth factor A; VEGFR2, VEGF receptor 2; VSMCs, Vascular smooth muscle cells; WAT, White adipose tissue.

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1. Introduction

Obesity is a major health challenge worldwide, and is leading to type 2 diabetes, atherosclerosis, cancer and increased mortality [1,2]. The complex pattern of genetic and lifestyle associated factors contributing to obesity is only partially understood. Visceral adiposity and central fat accumulation are associated with a higher risk for morbidity and mortality than subcutaneous adiposity [3–6]. A better understanding of the pathophysiological mechanisms underlying visceral obesity and adipose tissue remodeling is of great importance.

The inhibitor of differentiation-3 (*Id3*) gene was first discovered in 1991 in mice and was shown to code for the helix–loop–helix (HLH) protein ID3 [7]. In humans, the *ID3* (GenBank accession no. 3399) gene is located on chromosome 1 and consists of three coding exons and two introns. The ID3 protein is a 119 amino acid long, 15 kDa protein and is a member of the ID family of class V HLH proteins. Like other ID proteins (ID1, 2 and 4) ID3 has a helix–loop–helix region, but lacks the basic DNA-binding region characterizing most of the HLH proteins. Instead ID3 has a specific C-terminus essential for binding to other basic HLH (bHLH) proteins of which the most extensively examined are the class I bHLH proteins E12 and E47. Binding of ID3 to E12 and E47 prevents their dimerization with tissue specific class II bHLH proteins and subsequent binding to E-box consensus sequences (CANNTG) in the DNA [8–11] (Fig. 1).

Id3 plays an important role in normal embryonic development in rodents in interplay with *Id1* and *Id2* [12,13]. In adult rodents, *Id3* has been described as an early-responsive gene showing strongly increased levels of expression in response to growth factor stimulation [14], and the ID3 protein – as insinuated by its name – was first thought to be a general inhibitor of cell differentiation [14,15]. ID3 is indeed known to be involved in the differentiation of many cell types, including preadipocytes [15,16], fibroblasts [14] and myoblasts [11], but the role of ID3 as a global differentiation blocker has lately been questioned [17,18]. A huge range of regulatory mechanisms of and by *ID3* has been reviewed by Lim and Wu [19] and in this paper we will focus primarily on *ID3*'s role in angiogenesis and adipose tissue.

2. ID3 and angiogenesis

After initially focusing on the ID3 protein as a general inhibitor of differentiation, ID3 was later found to have more specific mechanisms. It stimulates angiogenesis in mice [13,17,20–23], and an interplay with the vascular endothelial growth factor A (*VEGFA*) seems evident even though the exact mechanism is not established. One paper suggests the effect to act through inhibition of E12's repression on the *VEGFA* promotor [17]. Other studies show VEGFA to induce *Id3* expression suggesting ID3 to act as a mediator of VEGFA actions [21,24]. Furthermore, ID3 regulates differentiation, proliferation and apoptosis of vascular smooth muscle cells (VSMCs). This effect is mediated via both E12 and E47; E12 stimulates the SMC differentiation marker gene SM α-actin by binding to E-box regions, thereby stimulating the differentiation of smooth muscle cells [9], and E47 activates transcription of cyclin-dependent kinase inhibitor 1 ($p21^{cip1}$) leading to apoptosis and decreased proliferation of VSMCs [25,26]. These mechanisms are antagonized by ID3 (Fig. 2).

Id3 and *Id1* have overlapping effects, and either *Id3* or *Id1* is required for intracerebral vascular development in mice embryos [13]. *Id1*/*Id3* double-knockout ($Id1^{-/-}/Id3^{-/-}$) mice embryos have decreased levels of VEGF, VEGF receptor 2 (VEGFR2), and smooth muscle α-actin in ganglionic vessels and cannot survive due to abnormal angiogenesis and intracerebral hemorrhage [13]. In adult mice, *Id3* expression (as well as expression of *Id1*, *2* and *4*) is down-regulated to undetectable levels in normal vasculature [13,25]. *Id3* – in interplay with *Id1* – is essential for tumor's ability to grow and metastasize, and the effect seems to be related to angiogenesis [13,20]. *Id3* has further been shown to be involved in growth and metastasis of malignant tumors through angiogenesis-driven mechanisms involving VEGF-mediated recruitment of bone marrow derived endothelial precursor cells [13,21,22].

Whether the mechanisms for ID3-regulated angiogenesis seen in mice are also present in humans is less clear. Some results point in the direction of ID3 playing a role in angiogenic regulation in humans: *ID3* is highly expressed in the endothelial cells of high-grade neuronal tumors [13], and ID3 plays a role in VEGF-stimulated angiogenesis in

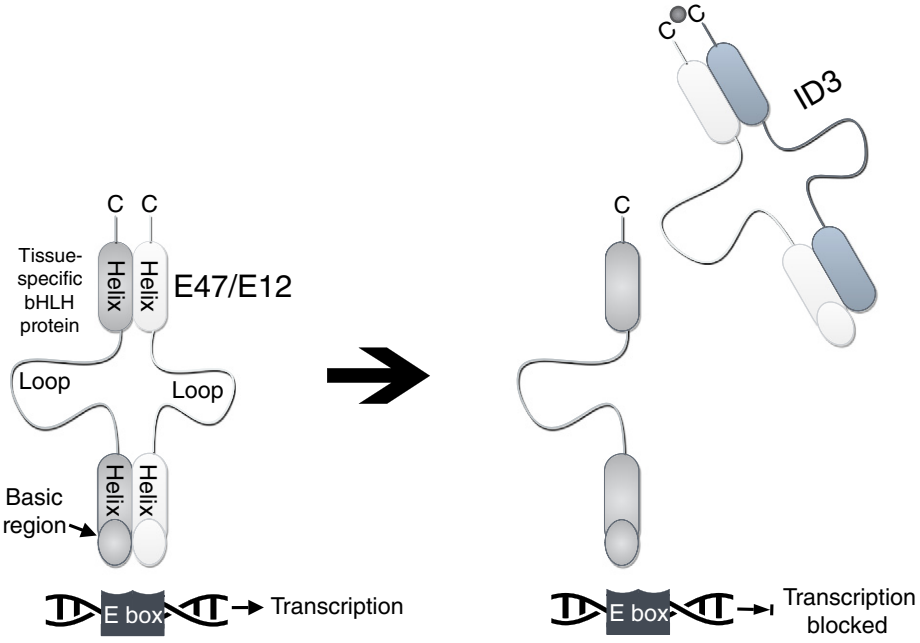

Fig. 1. ID3 binding of E12 or E47. The ID3 protein binds to the E-proteins E12 or E47 thereby preventing them from dimerizing with tissue-specific bHLH proteins subsequently preventing binding to E-boxes and gene transcription.