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The COP9 Signalosome Controls Adipocyte Differentiation by Regulating CHOP Protein Stability

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ABSTRACT

Obesity is a serious health problem of our time. Dysfunction of adipogenesis, the differentiation of adipocytes, is a hallmark of obesity. Therefore here we investigate the role of the COP9 signalosome and of CHOP in the differentiation of LiSa-2 preadipocytes.

Keywords: COP9 Signalosome; CHOP; Adipogenesis; Cullin-RING Ubiquitin Ligase

1. Introduction

Adipogenesis (differentiation of adipocytes) is a highly complex mechanism, closely cross-linked to the induction of angiogenesis which in turn promotes preadipocyte differentiation. Dysfunction of adipogenesis causes obesity. The process of adipogenesis is regulated by an elaborate network of transcription factors that coordinate the expression of hundreds of proteins responsible for establishing fat cell phenotype. In the centre of that network are the two master regulators of adipocyte differentiation, the peroxisome proliferator-activated receptor γ (PPAR-γ) and CCAAT/enhancer binding protein α (C/EBPα). Besides PPAR-γ, C/EBPα is considered a primary transcription factor that mediates adipogenesis. Early in the differentiation program C/EBPβ is expressed, which is the transcriptional activator of PPAR-γ and C/EBPα. Its activity is delayed by the C/EBP homologous protein (CHOP, also called growth arrest-DNA damage-induced 153, GADD153), a dominant negative form of C/EBP family members. CHOP dimerizes with adipogenic C/EBPs, suppresses their transactivation activity and, therefore, blocks adipogenesis. CHOP has to be down-regulated for the progression of the differentiation program. Interestingly, CHOP protein is degraded by the ubiquitin (Ub) proteasome system (UPS) and proteasome inhibitors stabilize the protein and block adipocyte differentiation [1].

2. Results

he COP9 signalosome (CSN) was first discovered in 1994 as a protein complex which negatively regulates photomorphogenesis in Arabidopsis [2]. It consists of 8 subunits (CSN1-8; depending on their size) and was detected in all eukaryotic cells. The CSN exhibits an extensive range of biological responses including embryonic development, cell cycle, signal transduction, apoptosis, DNA repair, homeostasis and also angiogenesis - all together reflecting the multifunctionality of the complex. The most important function of the CSN is the regulation of the activity of cullin-RING E3 Ub-ligases (CRLs) [3]. These ligases are the prominent transducers for protein degradation mediating the formation of a complex composed of the Ub carrying E2 conjugating enzyme and the substrate which is to be ubiquitinated. The CSN5 subunit of the CSN exhibits a metalloprotease activity, which can remove Nedd8 from CRLs, which regulates their activity [4].

Recently we have shown that the CSN is involved in adipogenesis [5]. Inhibitors of CSN associated kinases such curcumin and curcumin-like substances block the production of VEGF in tumor cells [6] as well as in adipocytes [5]. Inhibition of adipocyte VEGF production is one explanation for the fact that obesity can be downregulated by curcumin and resveratrol [7], although the exact mechanism remained obscure.

Here we show that the curcumin-like compound piceatannol induces CHOP in LiSa-2 preadipocytes, which blocks the process of adipocyte differentiation. CHOP is targeted for degradation via UPS by the CSN and permanent downregulation of the CSN in LiSa-2 cells inhibits adipogenesis by stabilizing CHOP. Permanent overexpression of Flag-CHOP causes a similar phenotype as downregulation of the CSN. The CRL responsible for CHOP Ubiquitination was identified.

3. Conclusions

CHOP is an important regulator of adipogenesis. The COP9 signalosome is essential for the differentiation of adipocytes.

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