

Signaling networks

Important proteins of signaling networks are found to be specifically expressed during adipogenesis (Fig. 4). Known and hypothetical functional aspects of transcriptionally regulated targets with relevance for adipogenesis are discussed below.

Known regulators of cell division are not repressed only during the clonal expansion phase. Activator of S phase kinase (Ask, No. 359) is the regulatory subunit of Cdc7 kinase and recruits it to the minichromosome maintenance protein complex and the origin recognition complex. The Cdc7 kinase activity is co-regulated with the Ask expression [1]. Vaccinia related-kinase 1 (Vrk1, No. 267) is shown to phosphorylate p53 and considered to act as a switch controlling p53 binding partners [2]. Many known GTPase-pathway associated genes have been measured as highly expressed after induction. T-lymphoma invasion and metastasis 1 (Tiam1, No. 159) is a guanine nucleotide exchange factor (GEF) of the small GTPase Rac1, which regulates actin cytoskeleton, morphology and adhesion and antagonizes RhoA signaling [3,4]. Additionally, the putative constitutive active Rho GTPase Wnt1 responsive Cdc42 homolog (Wrch-1, No. 292), which has no detectable intrinsic GTPase activity and very high nucleotide exchange capacity, leads to an up-rounded phenotype [5,6]. Interplay between Wrch-1 and Tiam1, which might reverse the Wrch-1 activity through Rac1 signaling [5], could be a regulatory mechanism of cell morphology in adipogenesis. The small GTPase Rab1 (No. 325) regulates the transport of newly synthesized proteins from the rough endoplasmic reticulum to the Golgi [7,8]. Ras GTPase-activating protein III (GAPIII, No. 63) is a negative regulator of ras, which controls proliferation and differentiation in many cell [9]. We find the regulator of G-protein signaling 2 (Rgs2, No. 44) permanently up-regulated. Its high expression has been observed during early adipogenesis [10].

16 receptors are strongly transcriptionally regulated during adipogenesis (Fig. 3). Further proteins, which ensure the availability and function of receptors, have a distinct expression profile. Low density lipoprotein receptor-related protein associated protein 1 (Lrpap1, No. 28) and receptor (calcitonin) activity modifying protein 2 (Ramp2, No. 266) are both in the mainly up-regulated cluster 9. Lrpap1 prevents co-expressed ligands to bind prematurely to the LDL-receptor family during procession and supports receptor folding [11-13]. Ramp2 controls the transport and glycosylation of the calcitonin receptor, which modifies the receptor to be adrenomedullin specific [14]. We find the peptide hormone adrenomedullin (AM, No. 314) strongly repressed after 12 hours. This contrasts a recent observation of a U-shaped regulation profile [15]. Nuclear receptor interacting protein 1 (RIP140, No. 8) can bind to adipogenic transcription factors PPAR and RXR [16,17] and can regulate energy homeostasis in white adipose tissue [18]. Parallel to transforming growth factor β 3 (TGFbeta3, No. 574), decorin (No. 137/623) is strongly overexpressed during whole adipogenesis. Although expression of TGFbeta3 was found in mature adipose tissue [19], TGF- β is a potent inhibitor of adipogenesis [20]. Beside stabilizing fibrils and orienting fibrillogenesis [21], the protein core of decorin can bind TGF- β [22]. On the one hand, this interaction can repress myogenesis [23] and, on the other, it can reverse repressive effects of autocrine TGF- β on mouse macrophage activation [24]. This mechanism might be important for adipogenic differentiation.

Possibly, up-regulation of Sult1a1 links thyroid hormone deactivation with increased lipogenic activity. Sulfotransferase, phenol preferring 1 (Sult1a1, No. 375) is the functional ortholog to the human SULT1A1. The latter is described to transfer sulphate to the thyroid hormone and to detoxify the cell [25] (it should be noted that the rat homologue is not known to use TH as substrate [26]). Sulphated T4S blocks the conversion to the bioactive T3 completely and enhances the conversion to the receptor-inactive reverse T3 (rT3) [27]. Hypothyroid concentrations (possibly mediated by Sult1a1) stimulate differentiation and the activity of lipogenic enzymes, whereas hyperthyroidism enhances thermogenesis and oxygen consumption [28,29]. Finally, TH receptor α (Thra, No. 438) might compete with PPAR for RXR if TH is present [30].

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