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Mini-review

Hedgehog and adipogenesis: Fat and fiction

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Abstract

Morphogenes, abundantly described during embryogenesis have recently emerged as crucial modulators of cell differentiation processes. Hedgehog signaling, the dysregulation of which causing several pathologies such as congenital defects and cancer, is involved in several cell differentiation processes including adipogenesis. This review presents an overview of the relations between Hedgehog signaling, adipocyte differentiation and fat mass. While the anti-adipogenic role of Hedgehog signaling seems to be established, the effect of Hedgehog inhibition on adipocyte differentiation *in vitro* remains debated. Finally, Hedgehog potential as a pharmacological target to treat fat mass disorders is discussed.

Keywords: Hedgehog signaling pathway; Gli1; Ihh; Adipocyte differentiation; Fat mass; Obesity; Lipodystrophy

1. Introduction

Dysregulation of adipose tissue mass is a major health-problem of the 21st century. Obesity, characterized by an excess of adipose mass, is associated with pathologies such as diabetes or hypertension. Its prevalence has tripled in many countries since 1980s and the incidence of both morbid and infantile obesity is alarming. On the other hand, lipodystrophies, characterized by a modification of quantity and/or repartition of adipose mass, are also associated with diabetes and hyperlipidemia. The use of polytherapies for the treatment of Human Immunodeficiency Virus infected patients has been associated with an increase in the incidence of lipodystrophy this last twenty years. Indeed, while polytherapies, which consist in protease inhibitors and reverse transcriptase inhibitor analogues, have raised life expectancy of most patients, half of them are affected with a lipodystrophic syndrome.

Alterations in fat mass frequently involve dysregulation of adipocyte differentiation. To investigate this phenomenon, various cellular and animal models have been developed [1,2]. Preadipocyte cell lines such as 3T3-L1 or 3T3-442A have been used extensively to elucidate transcriptional cascades leading to an adipocyte phenotype. These cells have allowed to identify PPARγ and C/EBPα as key transcriptions factors of adipogenesis [2]. They induce the expression of most of the adipogenic genes. Molecular events involved in earlier step of differentiation are now under scrutiny. Pluripotent cells such as embryonic stem cells and mesenchymal multipotent cells such as calvaria cells, C3H10T1/2 or stromal cells from adipose tissue or bone marrow are powerful tools to investigate mechanisms involved in the commitment towards the adipocyte lineage.

Recently, morphogenes such as Wnt, Hedgehog, Notch and Transforming Growth Factor (TGF), the function of which having abundantly been described during embryogenesis, have emerged as crucial modulators of cell differentiation processes, including adipogenesis. In particular, Hedgehog signaling pathway is essential for many organ specifications and cell fates during embryogenesis. Disorders of this signaling pathway are associated with several congenital defects such as holoprosencephaly or polydactyly. Recent studies indicate that Hedgehog pathway is also active in some adult tissues where it regulates stem cell maintenance and differentiation. Its role is well characterized for instance in neurogenesis,

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osteogenesis and chondrogenesis [3–6]. Hedgehog uncontrolled activation is associated with various hereditary or sporadic cancers formation, survival and growth [7–10].

In this review, we will focus on Hedgehog signaling pathway status and implication in adipogenesis and will discuss its potential as a pharmacological target to treat fat mass disorders.

2. Hedgehog signaling pathway

Hedgehog pathway is activated by the fixation of one of the three mammalian ligands: Sonic Hedgehog (Shh), Indian Hedgehog (Ihh) or Desert Hedgehog (Dhh) to the receptor Patched (Ptc), a 12 transmembrane spanning protein. Shh, Dhh and Ihh are the product of genic duplication of the unique Hh ligand present in Drosophila. They are lipid-modified proteins produced in different organs, during embryogenesis and in the adult. For instance, Ihh is found in the hypertrophic chondrocytes, Shh in the haematopoietic stem cells and Dhh in the testis. So far, no obvious difference in the signaling pathway of these three ligands has been described.

In absence of ligand (Fig. 1), Smoothened (Smo), a 7 transmembrane spanning protein with homology to G-protein coupled receptors, is inhibited by Ptc and cannot activate the transduction cascade. In this condition Gli2/3, which are Krüppel-like zinc finger transcription factors, are polyphosphorylated and proteolytically processed *via* the proteasome before their translocation into the nucleus in a repressor form (GliR).

Ligand binding released Smo from Ptc inhibition. This leads to an activation of a not totally elucidated pathway that results in Gli stabilization and translocation into the nucleus (for more details see refs. [11–15]). Gli1 is one of Hedgehog target genes and has been characterized as a reliable marker of Hedgehog signaling activity. Its expression level reflects the activity state of the pathway.

In vertebrate, recent studies have suggested that the complex of protein downstream of Smo is formed in a particular microtubular structure that protrudes from the surface of most vertebrate cells called the primary cilium. The importance of this organelle is highlighted by the observation that mutation of intraflagellar transport proteins, crucial for primary cilium formation, lead to an altered Hedgehog signaling [12,16,17]. In addition, Bardet-Biedl syndrome, a genetic disorder associated with ciliopathy is characterized by several features including polydactyly, kidney anomalies, which are reminiscent of pathologies associated with Hedgehog signaling malfunction [18,19].

3. Activation of Hedgehog signaling inhibits adipocyte differentiation

Anti-adipogenic properties of Hedgehog signaling have been clearly evidenced *in vitro* on murine cells (Table 1). First observations were performed on mesenchymal cells able to differentiate into both adipocyte and osteoblast lineages such as calvaria cells or C3H10T1/2 and KS483 cell lines. Activation

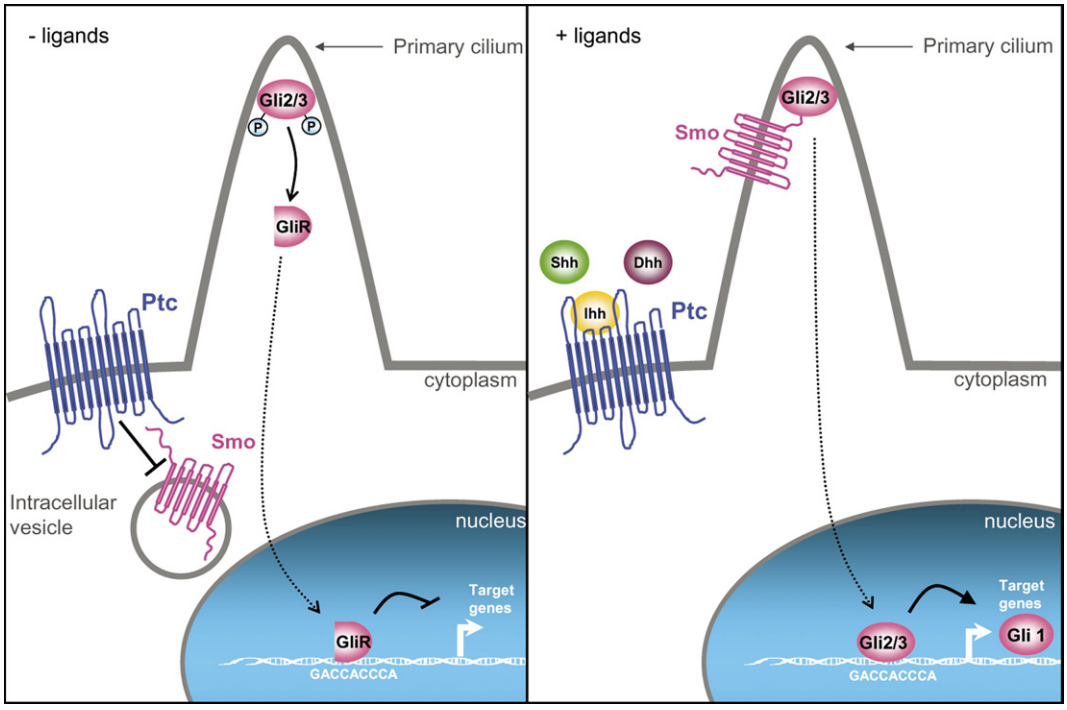

Fig. 1. Hedgehog signaling pathway. In absence of ligand Ptc inhibits Smo, localized into intracellular vesicle. Gli2/3, located at the extremity of the primary cilium, are phosphorylated and targeted to the proteasome to be processed into Gli repressor form (GliR). GliR translocates to the nucleus to inhibit target genes. When the pathway is stimulated by the binding of a ligand (Ihh, Shh or Dhh) to the receptor Ptc, Smo is no more inhibited and targeted to the primary cilium. The transduction cascade is activated to inhibit Gli phosphorylation and processing. Gli transcription factors, in their activated form, translocate into the nucleus and activate targets genes expression, Gli1 being one of them.