Review

CellPress

Notch signaling as a novel regulator of metabolism

Pengpeng Bi[1] and Shihuan Kuang[1,2]

[1] Department of Animal Sciences, Purdue University, West Lafayette, IN 47907, USA
[2] Center for Cancer Research, Purdue University, West Lafayette, IN 47907, USA

Evolutionarily unprepared for modern high-calorie diets and sedentary lifestyles, humans are now unprecedentedly susceptible to metabolic disorders such as obesity, type 2 diabetes (T2D), nonalcoholic fatty liver, and cardiovascular disease. These metabolic conditions are intertwined, together known as metabolic syndrome, and compromise human life quality as well as lives. Notch signaling, a fundamental signal transduction pathway critical for cell–cell communication and development, has recently been recognized as a key player in metabolism. This review summarizes the emerging roles of Notch signaling in regulating the metabolism of various cell and tissue types, with emphasis on the underlying molecular mechanisms and the potential of targeting this signal axis to treat metabolic diseases.

An overview of Notch signaling

The Notch signaling pathway is an evolutionarily conserved pathway important for cell–cell communication and cell-fate determination during development and is required for adult tissue homeostasis. It comprises Notch receptors (see Glossary) and Notch ligands as well as intracellular proteins that function to transmit the Notch signal to the cell's nucleus. Notch receptors (Notch1–4) are single-pass transmembrane proteins comprising an extracellular domain (NECD), a transmembrane (TM) domain, and an intracellular domain (NICD). Notch ligands are also transmembrane proteins and cells expressing Notch ligands must be in close proximity to Notch-expressing cells for signaling to occur. Ligands bind to the Notch NECD to induce proteolytic cleavage and release of the NICD, which enters the cell nucleus to modify gene expression. Notch ligands are members of the Delta/Serrate/LAG-2 (DSL) family of proteins that includes Delta-like (Dll1, Dll3, Dll4) and Jagged (Jag1, Jag2) in mammals [1,2].

Notch signal transduction is initiated on binding of a Notch receptor to a ligand located on a neighbor cell. Endocytosis of Notch-bound ligand generates a mechanical pulling force that drives conformational changes of the Notch receptor and facilitates its sequential proteolytic cleavage [3]. The first cleavage, mediated by a disintegrin and metalloproteinase (ADAM) family peptidase, releases the NECD, whereas the second cleavage, mediated by γ-secretase, releases the NICD [1]. The NICD then translocates to the nucleus where it binds with recombination signal binding protein for immunoglobulin kappa j region (Rbpj) and recruits a transcriptional complex to activate the transcription of downstream targets including Hairy/enhancer of split (Hes) and Hes-related with YRPW motif protein family genes. Simple in design, activation of Notch is tightly orchestrated at multiple levels [1] and the

Glossary

Atherosclerosis: a type of vascular disease characterized by plaque accumulation in arteries resulting from increased cytokines due to metabolic dysfunction, which leads to activation of the innate immune system and chronic inflammation.
Beige adipocytes: a newly defined type of adipocyte within the WAT. They are similar to brown adipocytes in that they express UCP1 and have the capacity for thermogenesis. Their gene expression signature is distinct from those of both brown adipocytes and white adipocytes.
Brown adipocytes: a type of adipocyte that is abundant in rodents and newborn humans but less abundant in adult humans and has a high capacity for adaptive thermogenesis. Brown adipocytes contain numerous mitochondria expressing UCP1, which uncouples the proton gradient from ATP production to generate heat. Due to their ability to burn lipids (through β-oxidation) to generate heat, brown adipocytes increase energy expenditure and are negatively associated with obesity.
Delta/Serrate/Lag-2 (DSL) family protein: single-pass transmembrane proteins whose extracellular domain acts as a ligand for Notch receptors on a neighboring cell. In mammals, the family members include Delta-like (Dll1, Dll3, Dll4) and Jagged (Jag1, Jag2).
Gluconeogenesis: a biochemical process that generates glucose from non-carbohydrate carbon substrates like pyruvate.
Glycogenolysis: a biochemical process whereby glycogen is broken down to glucose 1-phosphate.
Glycolysis: a biochemical process that converts glucose to pyruvate, releasing free energy in the form of ATP.
Hairy/enhancer of split (Hes): a transcription repressor that belongs to the bHLH protein family with important roles in the Notch signaling pathway.
Hes-related with YRPW motif protein (Hey): a nuclear protein that belongs to the Hes-related (HESR) family of basic helix–loop–helix (bHLH)-type transcriptional repressors. Hey expression is induced by Notch signaling.
Lipogenesis: a metabolic pathway that has two separate processes: fatty acid synthesis and triglyceride synthesis.
M1 and M2 macrophages: also known as classically and alternatively activated macrophages, respectively. M1 macrophages are activated in response to bacterial infections or lipopolysaccharide and IFN-γ and are highly inflammatory. By contrast, M2 macrophages are activated in response to parasitic infections or IL-4 and -13 and are anti-inflammatory.
Notch receptors (Notch1–4): a family of single-pass transmembrane receptors comprising an NECD, a TM domain, and an NICD. Activation of Notch receptors leads to release of the NICD, which then acts as a transcription factor to regulate gene expression.
Recombination signal binding protein for immunoglobulin kappa j region (Rbpj): also known as CBF1 in humans; a highly conserved DNA-binding protein that mediates canonical Notch signaling.
White adipocytes: a major type of adipocyte in animals and humans that store energy in the form of triglycerides.

Corresponding authors: Bi, P. (pbi@purdue.edu); Kuang, S. (skuang@purdue.edu).
Keywords: notch signaling; obesity; type 2 diabetes; insulin resistance.

1043-2760/
 http://dx.doi.org/10.1016/j.tem.2015.02.006

biological output is highly cellular-context dependent. One unique and important feature of Notch signaling is the lack of secondary amplification: NICD is part of the Notch receptor as well as the direct activator of Notch targets. Therefore, every event of Notch activation engages and consumes one Notch receptor. A similar turnover scenario also applies to Notch ligands. Notch ligand and receptor turnover together establish an oscillating pattern of Notch activation based on the availability of replenished Notch receptors and ligands. Nuclear NICD is eventually targeted for proteasomal degradation mediated by the E3 ubiquitin ligase F box- and WD repeat domain-containing 7 (FBW7) [4,5]. A recent study showed that FBW7 transcription is repressed by the Notch target gene Hes5, thus creating a positive feedback loop that prolongs Notch signaling [6].

Notch signaling is a highly conserved intercellular communication mechanism critical for many cellular processes including survival, proliferation, and differentiation, as well as maintaining stem cell quiescence and identity [7]. Thus, Notch signaling is widely employed to orchestrate proper development and perturbation of the Notch pathway is linked to various devastating genetic disorders and cancers [8]. In addition, recent studies employing transgenic mouse models of tissue-specific manipulation of Notch signaling have begun to reveal the roles of the Notch pathway in regulating metabolism in several key metabolic organs.

Notch signaling in diabetic and fatty liver

Notch signaling is involved in embryonic development, postnatal regeneration, and carcinogenesis of the liver [9], the central hub for glucose and lipid metabolism. On feeding, an increase in blood glucose stimulates the secretion of insulin from the pancreas. Circulating insulin inhibits liver glucose production, including glycogenolysis and gluconeogenesis, and stimulates glucose utilization, including glycolysis and lipogenesis. Recent studies have revealed a key role of Notch signaling in regulating both processes, with abnormal activation of Notch signaling in hepatocytes leading to hyperglycemia and fatty liver disease (Figure 1) [10,11].

The effect of Notch signaling on hepatic glucose production is mainly mediated through synergy of NICD with the transcription factor forkhead box protein O1 (FoxO1) (Figure 1). FoxO1 directly activates the transcription of the catalytic subunit of glucose-6-phosphatase (G6pc), a rate-limiting enzyme involved in hepatic glycogenolysis and gluconeogenesis [11]. Compound haploinsufficiency of FoxO1 and Notch1 ($Foxo1^{+/-}$:$Notch1^{+/-}$) markedly ameliorates insulin resistance in diet-induced obese (DIO) mice [11]. Liver-specific knockout of *Rbpj* using albumin-Cre phenocopies FoxO1:Notch1 haploinsufficiency, indicating that Notch signaling is the key driver of hepatic insulin resistance. Consistently, adenovirus-mediated activation of Notch1 in liver induces G6pc expression and exacerbates insulin resistance in a FoxO1-dependent manner [11].

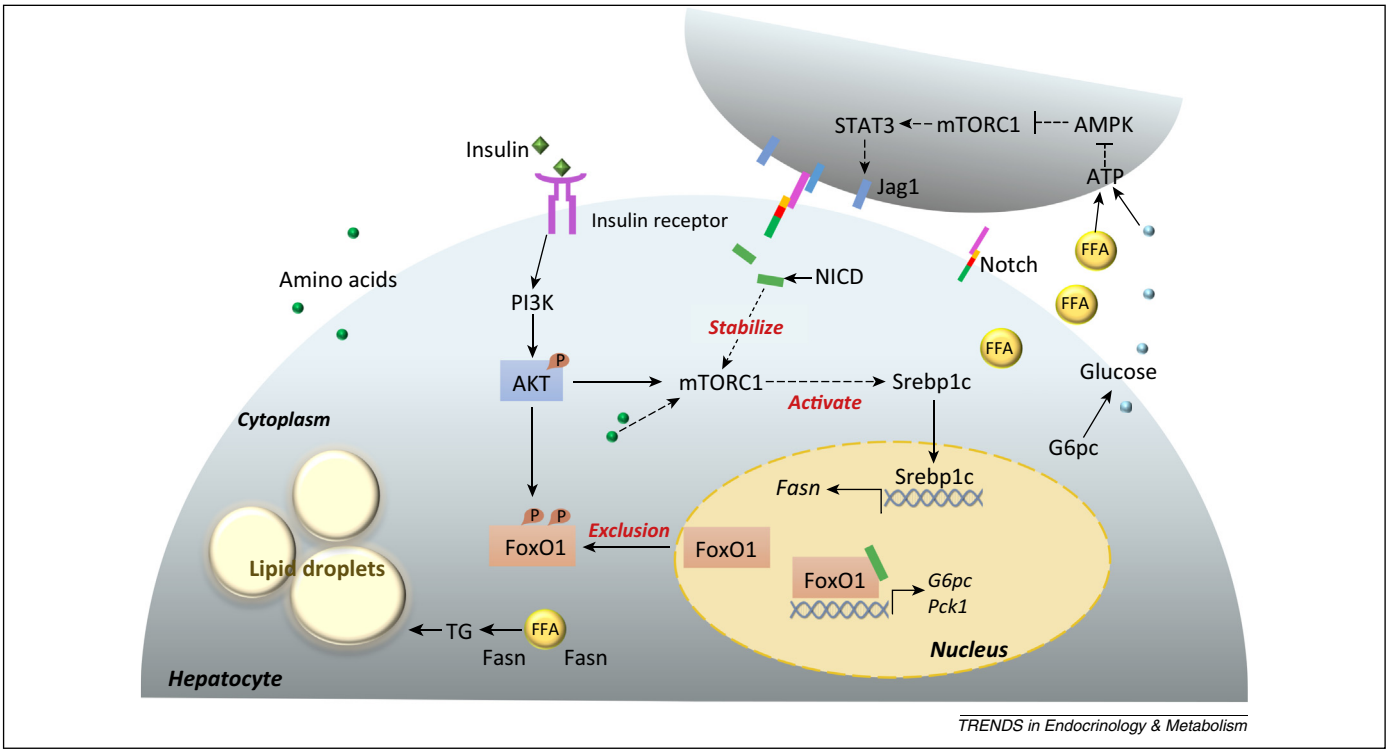

Figure 1. Notch regulates gluconeogenesis and lipogenesis of hepatocytes. Notch signaling regulates hepatic glucose production through synergy with forkhead box protein O1 (FoxO1), which directly activates the transcription of glucose 6-phosphatase, catalytic subunit (G6pc) and phosphoenolpyruvate carboxykinase 1 (Pck1), the rate-limiting enzymes in hepatic glycogenolysis and gluconeogenesis, respectively. Transcriptionally active FoxO1 is phosphorylated by AKT and excluded from the nucleus. In addition, Notch signaling promotes hepatic lipogenesis through an unknown factor that stabilizes mammalian target of rapamycin complex 1 (mTORC1), which is normally activated by amino acids, as well as the insulin–phosphatidylinositol-3-kinase (PI3K)–AKT pathway. mTORC1 in turn activates sterol regulatory element-binding protein 1c (Srebp1c), a key factor that turns on the transcription of fatty acid synthase (Fasn), which encodes a rate-limiting enzyme in lipogenesis. In obesity, high levels of glucose and free fatty acids (FFAs) activate the AMP-activated protein kinase (AMPK)–mTORC1–signal transducer and activator of transcription 3 (STAT3) pathway, which eventually upregulates Jagged 1 (Jag1) and activates Notch signaling in the neighboring hepatocyte. Broken line indicates indirect effect. Abbreviation: TG, triglyceride.