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Review

FoxO1, the transcriptional chief of staff of energy metabolism

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ABSTRACT

FoxO1, one of the four FoxO isoforms of Forkhead transcription factors, is highly expressed in insulin-responsive tissues, including pancreas, liver, skeletal muscle and adipose tissue, as well as in the skeleton. In all these tissues FoxO1 orchestrates the transcriptional cascades regulating glucose metabolism. Indeed, FoxO1 is a major target of insulin which inhibits its transcriptional activity via nuclear exclusion. In the pancreas, FoxO1 regulates β-cell formation and function by a balanced dual mode of action that suppresses β-cell proliferation but promotes survival. Hepatic glucose production is promoted and lipid metabolism is regulated by FoxO1 such that under insulin resistance they lead to hyperglycemia and dyslipidemia, two features of type 2 diabetes. In skeletal muscle FoxO1 maintains energy homeostasis during fasting and provides energy supply through breakdown of carbohydrates, a process that leads to atrophy and underlies glycemic control in insulin resistance. In a dual function, FoxO1 regulates energy and nutrient homeostasis through energy storage in white adipose tissue, but promotes energy expenditure in brown adipose tissue. In its most recently discovered novel role, FoxO1 acts as a transcriptional link between the skeleton and pancreas as well as other insulin target tissues to regulate energy homeostasis. Through its expression in osteoblasts it controls glucose metabolism, insulin sensitivity and energy expenditure. In a feedback mode of regulation, FoxO1 is also a target of insulin signaling in osteoblasts. Insulin suppresses activity of osteoblastic FoxO1 thus promoting beneficial effects of osteoblasts on glucose metabolism. The multiple actions of FoxO1 in all glucose-regulating organs, along with clinical studies suggesting that its glycemic properties are conserved in humans, establish this transcription factor as a master regulator of energy metabolism across species.

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Contents

Introduction

Glucose homeostasis is a finely tuned process comprised of glucose production and uptake by several organs, with the pancreas and liver being the main stimulators or inhibitors of glucose production. Pancreatic β-cells rapidly sense elevations in blood glucose levels and respond by increasing insulin production through increased proliferation. The liver maintains blood glucose levels through two processes: gluconeogenesis, generation of glucose from non-carbohydrate carbon substrates, and glycogenolysis, degradation of glycogen. Skeletal muscle also regulates energy metabolism by contributing to more than 30% of resting metabolic rate and 80% of whole body glucose uptake. Adipocytes regulate energy homeostasis either through secretion of cytokines controlling appetite and insulin sensitivity or by storing

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excess amount of energy intake as triglycerides and mobilizing them to be oxidized during energy deprivation.

Until recently it was well accepted that glucose levels and energy expenditure are tightly coregulated by the classic peripheral insulin-producing or insulin-sensing organs. However, during the last few years, another organ has emerged as a potent regulator of energy metabolism, the skeleton [1–3]. In addition to its homeostatic properties during bone growth, the skeleton serves a novel endocrine function as a regulator of whole body glucose metabolism. In this task the skeleton regulates energy metabolism by favoring β-cell proliferation, insulin secretion, insulin sensitivity and energy expenditure. In addition, it is itself a target of insulin signaling [2,4]. Osteoblasts possess an intricate array of functions that control glucose metabolism through the secretion of the osteoblast-specific Osteocalcin, the activity of which is regulated in a bimodal mode of action. At the transcriptional level through suppression of the expression of *Esp*, a gene encoding a tyrosine phosphatase, which suppresses osteocalcin metabolic activity by promoting its carboxylation [5,6]. In addition insulin receptor (InsR) signaling in osteoblasts induces *Osteocalcin* expression by relieving the inhibitory effect of the transcription factor Twist2 on Runx2, a main regulator of *Osteocalcin* expression [2]. At the activity level, through direct regulation of osteocalcin carboxylation by another energy consuming function of the skeleton: bone resorption [4]. In a leap forward from the studies in rodents, many clinical studies have suggested that osteocalcin is a marker of glucose tolerance [1,2,7–10].

Demonstrating the pivotal role of bone in the control of energy homeostasis, recent evidence suggests that other hormones, in addition to osteocalcin may be mediating this endocrine function [3]. Indeed, partial osteoblast ablation in mice compromises glucose homeostasis and demonstrates that the skeleton potently regulates all determinants of energy metabolism: glucose and insulin production, glucose tolerance and insulin sensitivity, fat metabolism, energy expenditure and appetite in both osteocalcin-dependent and independent manners. The notion of an additional, bone-derived hormone regulating glucose metabolism is in line with the fact that other organs utilize more than one secreted molecules to affect body functions Remarkably for the skeleton, the exact same transcriptional mediator of insulin actions in all insulin-sensitive target organs also regulates the metabolic activity of osteocalcin and its insulin-upregulating as well as insulin-sensitizing actions: FoxO1 [6]. Thus, FoxO1 becomes a common unifying link of insulin signaling among all glucose-regulating organs (Fig. 1).

It is the dominant role of insulin signaling in all glucose-regulating organs that originally brought to light the Forkhead box O (FoxO) family of transcription factors. Among all transcription factors involved in energy regulation, the FoxO proteins, and more in particular FoxO1, are the main transcriptional modulators of insulin actions. Insulin suppresses FoxO1 activity through activation of the PI3K/AKT signaling pathway. Activated AKT phosphorylates FoxO1 at 3 highly conserved phosphorylation sites resulting in its nuclear exclusion and thus inhibition of transcription [11]. There are three additional FoxO proteins

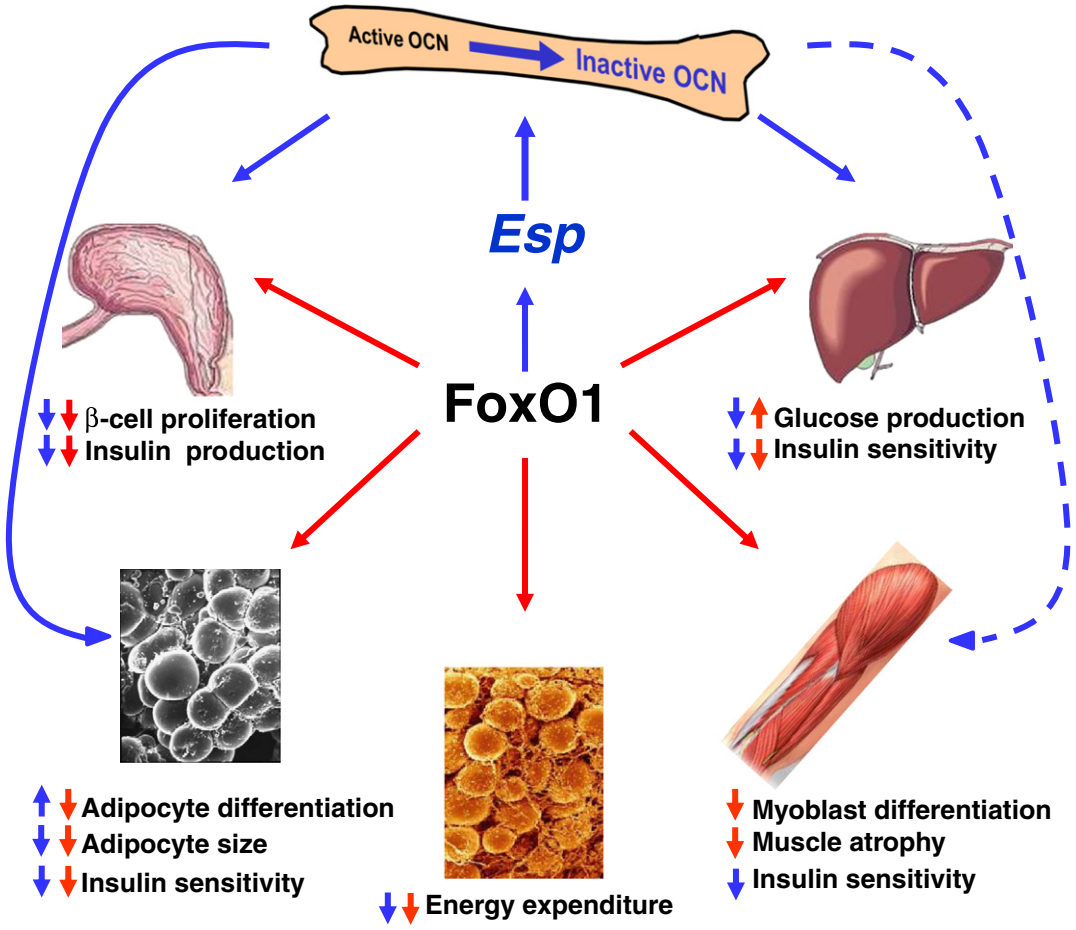

Fig. 1. FoxO1 is a unifying regulator of energy metabolism through the skeleton and peripheral organs. FoxO1 promotes glucose production by suppressing β-cell proliferation and insulin synthesis, by suppressing insulin sensitivity in the liver and white adipose tissue and by inducing expression of gluconeogenic enzymes. In the muscle, FoxO1 inhibits myoblastic differentiation but provides energy, when supplies are low, through breaking down of muscle protein leading to muscle atrophy. In white and brown adipose tissue FoxO1 has a dual function: in the first it decreases insulin sensitivity and suppresses adipogenesis and adipocyte size thus regulating energy and controlling energy storage. In the latter it decreases energy expenditure. In bone FoxO1 acts on osteoblasts to suppress expression of *Esp* and promote carboxylation/inactivation of Osteocalcin (OCN). Glucose levels increase through suppression of insulin production, decreased insulin sensitivity in the liver, muscle and white adipose tissue and suppression of energy expenditure. Although it decreases mitochondrial activity in the muscle, it is presently unknown whether if affects lean mass.