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FGF21 takes a fat bite

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Abstract

Recent research exposed an intricate signaling network linking FGF21, PPAR γ , PGC-1 α , and adipocyte differentiation. While these findings define novel biological roles of FGF21 in adipose tissue, they also cast a shadow of doubt over its preconceived function as a fasting hormone.

The quest for secreted peptides with metabolic actions has identified a number of conserved auto/para/exocrine growth factors - including neuregulins (1), the platelet-derived growth factor (2) and members of the fibroblast growth factor (FGF) family (3) – with the ability to stimulate glucose uptake and regulate mitochondrial function in key metabolic tissues. Amongst them, FGF21 has taken the center stage, because its endocrine actions endow it with potential therapeutic uses.

FGF21 is a very unique FGF, with less than 35% homology to other family members (4). Unlike most other FGFs, FGF21 diffuses upon secretion and functions as a hormone. The expression of FGF21 is predominant in white adipose tissue (WAT), liver and pancreas (4, 5). Most of the circulating FGF21, however, originates from the liver. The fact that FGF21 is induced in murine livers by starvation (6, 7) and that many of its actions mimic fasting - induction of gluconeogenesis, fat oxidation and ketogenesis, coupled to a state of torpor (6-8) - suggested that FGF21 could be a starvation signal.

A flurry of recent reports, however, suggests that the concept of FGF21 as a starvation hormone only reflects one aspect of FGF21 biology, since feeding promotes FGF21 synthesis in the WAT (9, 10). Most likely, the activation of PPAR γ accounts for this upregulation, as thiazolidinedione (TZD) PPAR γ agonists induce FGF21 levels in WAT (5, 9, 11). Intriguingly, FGF21 also regulates PPAR γ activity by preventing its inhibition through the sumoylation of Lys¹⁰⁷ and, as a consequence, FGF21 null mice have less adipose tissue mass (9). In line with this, FGF21-KO mice are refractory to many of the effects of TZDs. For example, TZDs failed to increase adiposity and insulin sensitivity in FGF21-KO mice (9). The fact that FGF21 might favor adiposity is striking, as exogenous administration of FGF21 to animal models of diabetes is generally associated with weight loss (3, 12). Both the mechanistic link between FGF21 and PPAR γ sumoylation, as well as the physiological relevance of this sumoylation-dependent PPAR γ regulation require, however, further study. In this context, analysis of how local FGF21 production affects energy balance, lipolysis and adipocyte differentiation will be important to solve the apparent physiological discrepancies between localized versus systemic FGF21 increases. The generation of adipose tissue-specific FGF21-deficient mouse models, as well as PPAR γ

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sumoylation sites knock-in mice, will be key to understand these intriguing tissue-specific effects of FGF21.

Since PPAR γ activation inhibits bone formation (13, 14), bone fractures are one of the major comorbidities observed in patients treated with TZDs (15). Given the link between PPAR γ and FGF21, it is not surprising that pharmacological doses of FGF21 were found to induce severe bone loss by favoring the differentiation of bone marrow mesenchymal cells into adipocytes instead of osteoclasts; conversely, the lack of FGF21 enhances bone mass (16). Of note, the bone loss promoted by TZDs is prevented by FGF21 deletion (16), indicating that FGF21 not only contributes to the beneficial effects of TZDs on diabetes (9), but might also underpin some of the undesirable side effects, which also include cardiovascular and oncogenic complications (17-19). Further understanding of these facets of FGF21 biology is hence imperative to selectively channel the effects of TZDs away from these side effects.

Another twist in the unfolding role of FGF21 and adipocyte homeostasis came from its role in the browning of WAT in response to cold or adrenergic stimulation (20). This observation goes in line with previous studies linking FGF21 with thermogenic activity (21, 22). However, while FGF21 actions on neonatal brown fat function result from the regulation of systemic FGF21 levels (21), this does not seem to be the case for the browning of WAT as circulating FGF21 levels did not change upon cold exposure, suggesting auto/paracrine signaling (20). To promote browning FGF21 enhances PGC-1 α activity, potentially through inducing its post-translational modifications (20). Although the exact pathway through which FGF21 activates PGC-1 α and browning are not established, previous studies warrant scrutiny of the AMPK/SIRT1 signaling axis. In fact, the activation of AMPK and the subsequent SIRT1-mediated PGC-1 α deacetylation is reported to be essential for FGF21 to trigger PGC-1 α activity and enhance mitochondrial function (23). Pharmacological activation of AMPK is furthermore enough to enhance the browning of epididymal WAT, even though it is not clear whether this derives from a direct effect of AMPK in white adipocytes (24). Parallel studies show that the actions of FGF21 on hepatic lipid metabolism also require PGC-1 α (8), further suggesting that the activation of the AMPK/SIRT1 axis may be a general downstream feature linking FGF21 and PGC-1 α activity.

So, do these studies solve or expand the numerous questions that cast a shadow of doubt on the clinical use of FGF21? Human data have already established that FGF21 is not only a starvation hormone as FGF21 levels display no apparent circadian variation or a feeding/fasting cycle; only very prolonged fasting (7 days) increases plasma FGF21 (25). Furthermore, FGF21 levels are elevated in overweight patients with various features of the metabolic syndrome (26-28), potentially hinting to the existence of an obesity-induced FGF21-resistant state (29), even though this is debated (30). Future work will have to establish whether the local changes in adipose tissue FGF21 production, may actually contribute to the increase in circulating FGF21 observed in metabolic disease. Furthermore, the molecular and physiological pathways that endow FGF21 with the capacity to promote both white and brown fat tissue deserve further attention. Finally, it will be important to evaluate to what extent FGF21's thermogenic effects and PPAR γ activating effects respectively contribute to its beneficial effects on weight and glycemic control and how such improvements can be achieved while bypassing potential side effects, such as bone loss. These fascinating enigmas testify of our still rather primitive understanding of FGF21 biology, which for sure holds additional tricks up its sleeves.

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Figure 1. FGF21 systemic and local actions

New reports highlight how FGF21 can act in an auto/paracrine manner in white adipose tissue upon different stimuli.

Left arrow - Auto/paracrine effects: Feeding and PPAR γ agonists, such as TZDs, prompt local FGF21 expression in white adipocytes, which enhances the ability to store fat and contributes to the gain in fat mass induced by TZDs. Similarly, FGF21 mediates bone frailty induced by TZDs. Cold-exposure also promotes local FGF21 expression in the WAT, but in this case its action is driving the browning of white fat in order to improve thermogenesis.

Right arrow - Endocrine effects: The liver is the major source of circulating FGF21. Fasting or PPAR α agonists, such as fibrates, are the major stimulators of FGF21 release from the liver, which facilitates fasting-like adaptations, such as gluconeogenesis and fat oxidation, as well as thermogenesis in neonatal mice. Other tissues, such as brown fat upon cold exposure, can also release FGF21, although the impact of systemic FGF21 in this case is unknown