Cell Research (2012) 22:1416-1418.

www.nature.com/cr

RESEARCH HIGHLIGHT

The PPARγ-FGF1 axis: an unexpected mediator of adipose tissue homeostasis

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Cell Research (2012) **22**:1416-1418. doi:10.1038/cr.2012.94; published online 19 June 2012

Adipose tissue remodeling is a dynamic process during nutritional fluctuation that plays critical roles in metabolic homeostasis and insulin sensitivity. The process is highly regulated by many factors, including adipokines and cytokines that are locally released within fat pads. In a recent study published in *Nature*, Jonker and colleagues identified FGF1 as an important mediator that is selectively induced in fat cells by high-fat diet feeding and established the PPARγ-FGF1 axis as a critical pathway that regulates adipose tissue remodeling and ultimately systemic metabolic homeostasis.

An imbalance between energy intake and expenditure results in obesity, often a pathophysiological condition characterized by an excess of dysfunctional fat mass. The development of obesity is frequently associated with extensive adipose tissue remodeling that involves adipogenesis, angiogenesis, an enhanced build-up of extracellular matrix (ECM) and ultimately a pro-inflammatory local milieu [1]. Adipose tissue remodeling is governed by both genetic and nutritional components and can give rise to distinct types of tissue expansion with differential outcomes on metabolic fitness. A healthy tissue expansion entails an enlargement of adipose tissue through the dynamic recruitment of preadipocytes, along with an appropriate pro-angiogenic environment, well-controlled inflammatory responses and minimal ECM induction. In contrast, the more frequently observed unhealthy expansion consists of a rapid enlargement of existing adipocytes, limited/insufficient angiogenesis, the subsequent development of hypoxia, the induction of fibrosis and increased pro-inflammatory responses. This type of expansion is tightly associated with dysfunctional fat pads, which ultimately trigger systemic insulin resistance [1]. We have generated a number of genetic mouse models in which the remodeling is either facilitated (e.g., through the use of a collagen VI null mouse that has a less rigid extracellular matrix environment during a metabolic challenge [2]) or inhibited (by overexpression of a constitutively active form of HIF1α that causes chronic fibrosis [3]). Furthermore, remodeling can be impaired in chronically challenged animals that have their "metabolic flexibility" impaired, i.e., lose their ability to rapidly adjust to altered nutrient availability in adipose tissue. This metabolic inflexibility is associated with a lack of "immunological flexibility" during which there is a normal infiltration of M2-type macrophages into fasting adipose tissue, a phenomenon important for the necessary remodeling of adipose tissue during acute feeding/fasting cycles [4].

As an active secretory organ, adipose tissue releases a large number of factors including adiponectin, leptin, TNFα, vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) [5]. The relative rate of release of these factors is constantly modulated and at any given moment closely reflects the physiological state of a given fat pad, aiming to locally restore tissue homeostasis.

Among these factors, a group of proteins referred to as fibroblast growth factors (FGFs) represent a family of proteins that bind to and activate a unique set of tyrosine kinase receptors (FGFRs) [6]. These receptors stimulate downstream signaling events to regulate mitogenic, cytoprotective, angiogenic, tissue repair and other functions [7]. Due to their essential roles in diverse biological aspects, FGFs, especially paracrine FGFs, have been explored for their therapeutic potential [7]. FGF1 belongs to the subgroup of FGFs that act primarily in a paracrine fashion. Treatment of endothelial cells with FGF1 causes microvascular branching, suggesting a possible role in angiogenesis [8]. Intriguingly, as a proliferative factor, FGF1 may also play an important role in adipogenesis [9]. Due to its beneficial impact on the circulatory system, FGF1 has been tested for clinical applications in cardiovascular diseases

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[7]. Despite an extensive body of work on FGF1, the specific metabolic role of this growth factor highly enriched in adipose tissue remained unclear.

In a paper published in a recent issue of *Nature*, Jonker *et al*. highlight an essential role of FGF1 in adipose tissue remodeling [10]. They observed a robust and selective induction of FGF1 in gonadal white adipose tissue (gWAT) in response to high-fat diet (HFD) feeding [10]. This unexpected observation prompted them to further investigate the metabolic role of FGF1 by studying loss-of-function *Fgf1* null ($Fgf1^{-/-}$) mice. They and other groups did not observe a metabolic phenotype of $Fgf1^{-/-}$ mice when placed on a regular chow diet [11]. However, when fed with a HFD, $Fgf^{-/-}$ mice developed a profound diabetic phenotype, associated with severe peripheral insulin resistance and elevated inflammation [10], suggesting that FGF1 may be particularly relevant when nutritionally challenged. This is a situation similar to what can be observed with other key components affecting the ECM stability and rigidity, such as collagen VI null mice that do not display a distinct phenotype unless challenged with a HFD [2]. The other rather surprising finding is the specificity of the FGF1 induction that is for all practical purposes selective for gonadal adipose tissue and not seen in inguinal tissue. Gene expression patterns between different fat pads are conventionally distinct but closely related. To see an almost "digitized" read-out for FGF1 induction on the HFD in gonadal adipose tissue is rather unique. This raises the interesting question whether the induction of FGF1 is uniform within the gonadal fat pat or restricted to the tip of the fat pad that is usually rapidly expanding on a HFD.

What is the mechanism by which the loss of FGF1 triggers such a profound metabolic dysregulation? Our group recently demonstrated the importance of fully functional pro-angiogenic pathways for healthy fat pad remodeling. We achieved this by adipocyte-specific VEGF overexpression during a HFD challenge [12]. Since angiogenesis is a rate-limiting step during adipose tissue expansion [1], and since FGF1 has been reported to function as a modifier of endothelial cell migration and proliferation and has hence been postulated to be an angiogenic factor [13], Jonker and colleagues examined the vasculature in white adipose tissue (WAT) of $Fgf^{-/-}$ mice. They observed decreased vascular density and abnormal vascular structure specifically in gWAT. The impairment in vasculature further leads to a disruption of whole adipose tissue remodeling as a consequence of the need for expansion in response to nutritional stress induced by HFD. As a result, gWAT in the $Fgf^{-/-}$ mice fails to expand and exhibits a totally abnormal structure [10].

A hallmark of unhealthy adipose tissue expansion is hypoxia, which in turn stimulates an abnormally high level of fibrosis, ultimately triggering a more pro-inflammatory environment [1, 3, 14]. In line with these previous findings, they observed increased collagen deposition and a marked heterogeneity in adipocyte size in gWAT of $Fgf1^{-/-}$ mice upon HFD exposure. This was evident by histochemical analysis with Masson's trichrome stain, highlighting a high degree of pathological fibrosis in the mice. Furthermore, they saw in the null mice a dramatic increase in macrophage infiltration, accompanied by higher circulating MCP1 levels [10]. The pathological environment in these dysfunctional fat pads significantly affects the lipid storage function of the individual adipocyte. As a result, the free fatty acid release into circulation is increased and causes abnormal ectopic lipid accumulation in other tissues [1], including a significant elevation of hepatic steatosis in the FGF1-knockout mice [10]. Taken together, this cluster of phenotypic changes reported in response to the unhealthy fat tissue expansion in FGF1-knockout mice has been reported in other mouse models as well [3, 12, 14]. Notably, most dramatic functional deficiencies happen specifically in gWAT. Effects in other fat pads, such as inguinal WAT (iWAT) are very relatively minor. This differential response to a HFD challenge is consistent with previous observations [15].

Adipose tissue remodeling includes both expansion and contraction. The authors further verified that FGF1 also plays a critical role in adipose tissue contraction by re-adapting HFD-fed $FGF^{-/-}$ mice to regular chow (HCC). Both gross and histological examination of $Fgf^{-/-}$ HCC mice demonstrate that loss of function of FGF1 causes profound pathological changes in gWAT, demonstrating that FGF1 is dynamically required during both the expansion and contraction processes of adipose tissue [10].

What is the key transcription factor responsible for FGF1 induction in gWAT in response to HFD? It is reasonable to consider PPARγ (peroxisome proliferator-activated receptor γ) as a potential candidate, given that it is overall the master regulator of adipogenesis and plays an important role in the mature fat cell. Notably, there had been no reports suggesting that FGF1 is a direct transcriptional target for PPARγ. PPARγ is a ligand-dependent member of nuclear receptor superfamily of transcription factors. It was originally identified by Spiegelman and colleagues as an essential regulator of adipogenic differentiation [16]. PPARγ is induced during preadipocyte differentiation and maintained at high levels in both white and brown adipocytes. Thus, PPARγ not only serves as the master regulator of adipogenesis *per se*, but also regulates key metabolic genes in mature adipocytes. Of note, the important class of anti-diabetic drugs referred to as thiazolidinediones (TZDs) are potent transcriptional activators of PPARγ. Ligand activation of PPARγ by TZDs promotes the induction of a set of genes, such as CD36, aP2, PEPCK, LPL, and additional fatty acid transport proteins [16]. These genes regulate not only preadipocyte

differentiation, but also glucose and lipid metabolism, leading to improved insulin sensitivity. In addition, PPARγ also regulates adipokines, such as adiponectin, resistin, TNFα and MCP-1 levels. Furthermore, activation of PPARγ by TZDs can switch the subtypes of macrophages in adipose tissue from the more inflammatory M1 to M2 macrophages that lean more towards an anti-inflammatory and remodeling phenotype [16]. Much remains to be learned about the complex transcriptional changes triggered by various PPARγ agonists.

The report by Jonker *et al*. sheds light on this unexplored area. The findings suggest that FGF1 is a direct target of PPARγ. This functionally links two very important factors for adipose tissue physiology, the adipogenic master regulator PPARγ with an essential growth factor, FGF1. In the promoter region of the FGF1A transcript, a putative PPAR response element (PPRE) can be identified. They further verified these sites with luciferase reporter assays and ChIP-Seq methodology. Importantly, they also demonstrated that this PPARγ binding is adipocyte specific, and the adipocyte PPARγ-FGF1 axis is functionally conserved in mammals [10]. Intriguingly, they further confirmed the physiological relevance of the connection between FGF1 and PPARγ by treating the mice with the PPARγ ligand rosiglitazone, a TZD that used to be widely used clinically. They found that administration of rosiglitzone significantly upregulated the FGF1A transcript in gWAT. They further demonstrated PPARγ-driven FGF1 induction by showing that in adipose tissue-specific PPARγ-knockout mice, FGF1 levels decreased [10]. This novel identification of the PPARγ-FGF1 axis may explain some of the effects that TZDs exert in adipose tissue. These effects are rather complex. TZDs enhance local adipose tissue angiogenesis, and also effectively suppress inflammatory responses in adipocytes and macrophages. The results in this paper suggest that these effects may at least in part be through the modulation of the PPARγ-FGF1 axis.

These findings are timely and of importance, given that several other FGF family members have also recently been found to be regulated by nuclear receptors, and the regulation plays a positive role in energy homeostasis [10]. The data in this paper strongly highlights FGF1 as a direct target of PPARγ in HFD-fed mice. The loss-of-function mutant of FGF1 further emphasizes the critical role of FGF1 in adipose tissue remodeling and systemic metabolic homeostasis. However, the detailed mechanisms by which the PPARγ-FGF1 axis functions in fat pad remodeling still deserves further investigation. Further, the model used in this paper is a systemic FGF1-knockout mouse, making it challenging to distinguish primary effects in other tissues from local effects in adipose tissue. Thus functional effects in liver, muscle or other organs cannot be ruled out. In this sense, an adipose tissue-specific knockout might address this more directly. Nevertheless, this study not only emphasizes the continued importance of PPARγ as a drug target, but also underlines the therapeutic potential of FGF1 for metabolism-related disorders.

Acknowledgments

This work was supported by NIH grants (R01-DK55758, RC1DK086629, and P01DK088761) to P.E.S.

References

1 Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. *J Clin Invest* 2011; **121**:2094-2101.
2 Khan T, Muise ES, Iyengar P, *et al*. Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI. *Mol Cell Biol* 2009; **29**:1575-1591.
3 Halberg N, Khan T, Trujillo ME, *et al*. Hypoxia-inducible factor 1alpha induces fibrosis and insulin resistance in white adipose tissue. *Mol Cell Biol* 2009; **29**:4467-4483.
4 Wernstedt Asterholm I, McDonald J, Blanchard PG, *et al*. Lack of immunological fitness during fasting in metabolically challenged animals. *J Lipid Res* 2012; **53**:1254-1267.
5 Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. *Diabetes* 2006; **55**:1537-1545.
6 Mohammadi M, Olsen SK, Ibrahimi OA. Structural basis for fibroblast growth factor receptor activation. *Cytokine Growth Factor Rev* 2005; **16**:107-137.
7 Beenken A, Mohammadi M. The FGF family: biology, pathophysiology and therapy. *Nat Rev Drug Discov* 2009; **8**:235-253.
8 Uriel S, Brey EM, Greisler HP. Sustained low levels of fibroblast growth factor-1 promote persistent microvascular network formation. *Am J Surg* 2006; **192**:604-609.
9 Hutley L, Shurety W, Newell F, *et al*. Fibroblast growth factor 1: a key regulator of human adipogenesis. *Diabetes* 2004; **53**:3097-3106.
10 Jonker JW, Suh JM, Atkins AR, *et al*. A PPARgamma-FGF1 axis is required for adaptive adipose remodelling and metabolic homeostasis. *Nature* 2012; **485**:391-394.
11 Miller DL, Ortega S, Bashayan O, Basch R, Basilico C. Compensation by fibroblast growth factor 1 (FGF1) does not account for the mild phenotypic defects observed in FGF2 null mice. *Mol Cell Biol* 2000; **20**:2260-2268.
12 Sun K, Asterholm IW, Kusminski CM, *et al*. Dichotomous effects of VEGF-A on adipose tissue dysfunction. *Proc Natl Acad Sci USA* 2012; **109**:5874-5879.
13 Jaye M, Howk R, Burgess W, *et al*. Human endothelial cell growth factor: cloning, nucleotide sequence, and chromosome localization. *Science* 1986; **233**:541-545.
14 Hosogai N, Fukuhara A, Oshima K, *et al*. Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. *Diabetes* 2007; **56**:901-911.
15 Gesta S, Tseng YH, Kahn CR. Developmental origin of fat: tracking obesity to its source. *Cell* 2007; **131**:242-256.
16 Tontonoz P, Spiegelman BM. Fat and beyond: the diverse biology of PPARgamma. *Annu Rev Biochem* 2008; **77**:289-312.