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Mini review

Implications of Fibroblast growth factor/Klotho system in glucose metabolism and diabetes

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ABSTRACT

Diabetes mellitus, especially type 2 diabetes, remains the dominant metabolic disease worldwide, with an expected increase in prevalence of over 50% in the next 20 years. Our knowledge about the pathophysiology of type 2 diabetes continues to be incomplete, with unmet medical need for new therapies. The characterization of the fibroblast growth factor (FGF) family and the discovery of endocrine FGFs provided new information on the mechanisms of regulation and homeostasis of carbohydrate metabolism. More specifically, FGF19 and FGF21 signaling pathways have been linked to different glucose metabolic processes, including hepatic glucose synthesis, glycogen synthesis, glucose uptake, and insulin sensitivity, among others, and these molecules have been further related to the pathophysiology of diabetes mellitus. In-depth comprehension of these growth factors may bring to light new potential therapeutic targets for the treatment of diabetes mellitus.

1. Introduction

The incidence of Diabetes mellitus (DM), particularly type 2 diabetes (T2DM), which accounts for more than 90% of the cases, has increased dramatically, thereby reaching epidemic proportions. This disease is one of the major health concerns for the world population. The situation is extremely worrying, as the sedentary life style, the abundance of processed food and the increasing rate of childhood obesity will lead to an even higher prevalence of diabetes within the next years. A recent study estimated that the number of people with diabetes is expected to increase from 382 million in 2013 to 592 million by 2035; this represents a 55% increase in the prevalence of diabetes within 20 years [1].

To date, despite important advances over the last decades, our understanding of T2DM pathophysiology remains incomplete. In addition, there are concerns with current drugs, such as inadequate metabolic control, adverse effects and deficient prevention of diabetic complications, leading to an unmet medical need for new therapies. Latest elucidation of the fibroblast growth factor (FGF) family and their receptors and the implication of FGF19 and FGF21 in DM are attracting great attention. In this review, we provide an up-to-date report on the involvement of FGF19 and FGF21 in the regulation of glucose metabolism both from an experimental and clinical perspective, and we discuss potential therapeutic opportunities based on the FGF19 and FGF21 signaling pathways.

2. Fibroblast growth factors

The FGF superfamily consists of signaling peptides that participate in a broad diversity of biological processes, among them glucose metabolism. To date, 22 FGFs (FGF1–FGF23) have been identified in humans and categorized into seven subfamilies according to their phylogeny. In line with their mechanisms of action, these molecules were classified into intracrine, paracrine and endocrine FGFs [2].

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Paracrine (canonical) and endocrine (hormone-like) FGFs mediate biological responses by binding to and activating cell surface (tyrosine kinase) receptors termed FGF receptors (FGFRs). However, there is a relevant, structural feature in paracrine FGFs that is lacking in the endocrine forms, i.e. a heparin-binding domain. FGFRs for paracrine FGFs employ heparan sulfate (HS) as a cofactor, which in turn binds to the heparin-binding domain of the FGF molecule. HS in the extracellular matrix supports the paracrine mode of action and thereby leads to increased local effects. On the contrary, the lack of the heparin-binding domain in endocrine FGFs facilitates the release of these growth factors from their production sites and their role as hormone-like signaling molecules over long distances. Finally, intracrine (intracellular) FGFs act as mediators inside the cell without binding to any FGFR [2–5] (Table 1).

FGFs are expressed in almost any tissue and regulate main cellular processes in all stages of life. Accordingly, they are essential during embryogenesis, participating in the differentiation of the inner cell mass into the epiblast and endoderm lineages [6], as well organogenesis, where they regulate the development of organs like the brain, heart, lung, liver, kidneys, and the pancreas [7]. In the adult, FGFs participate in the regulation of cell survival, proliferation, migration, differentiation, and metabolism [7]. Of note, endocrine FGFs have a regulatory function in different metabolic pathways, including mineral, bile acid, lipid, and carbohydrate metabolism [7] (Table 2).

Table 1
Phylogenetic classification of fibroblast growth factors (FGF).

Subfamily	Molecule	Mechanism of action
FGF1	FGF1/FGF2	Paracrine/autocrine
FGF4	FGF4/FGF5/FGF6	
FGF7	FGF3/FGF7/FGF10/FGF22	
FGF8	FGF8/FGF17/FGF18	
FGF9	FGF9/FGF16/FGF20	
FGF11	FGF11/FGF12/FGF13/FGF14	Intracrine
FGF19	FGF19/FGF21/FGF23	Endocrine (hormone-like)

3. Fibroblast growth factor receptors

Four genes encode for FGFRs (FGFR1–FGFR4). Alternative splicing gives seven FGFR proteins with different ligand-binding specificity, i.e. FGFR1b, FGFR1c, FGFR2b, FGFR2c, FGFR3b, FGFR3c, and FGFR4 [8]. Binding of paracrine FGFs to the extracellular receptor domain, with HS as a cofactor, induces phosphorylation of the specific, cytoplasmic tyrosine residue and, as a result, activates the intracellular domain, which in turn couples the receptor to intracellular signal transduction pathways. The major substrate for FGFR kinase is FGFR substrate 2α. Activation of FGFR kinase triggers downstream signaling through the RAS–MAPK or PI3K–AKT pathway, generating primarily mitogenic and cell survival response. Activated FGFR kinase also recruits and activates phospholipase Cγ1, which in turn induces calcium release from intracellular stores and activation of calcium-dependent, cell motility-related signaling [7,9].

The lack of the heparin-binding domain in endocrine FGFs may be disadvantageous for FGFR activation at their target organs. However, endocrine FGFs use Klotho proteins rather than HS as a cofactor in order to enhance their affinity to their target organ receptors. The binding of endocrine FGFs to FGFRs with Klotho as a cofactor gives rise to FGF–FGFR-Klotho complexes, which then activate the FGFR tyrosine kinase [9].

4. Klotho proteins

At the end of the 1990s, the *klotho* gene was discovered by Kuro-o et al. [10] while studying the phenotype of transgenic mice, which overexpressed a different gene; they observed an accidental insertion of ectopic DNA in a region of the *klotho* gene, which inhibited its expression. The disruption of the *klotho* gene led to accelerated aging. Later, overexpression of *klotho* in mice was found to significantly delay aging and give rise to a longer lifespan [11].

Clotho, one of the goddesses (Fates or *Moirae*) who in Greek mythology controlled human destiny from birth to death, was the inspiration for the name of the new gene. Clotho was the spinner, she spun the thread of a person's life. In line with this myth, the name *klotho* represents a gene that somehow also seems to spin the thread of life.

The Klotho protein family comprises three members. The founder Klotho is named α-Klotho and shares homology with two proteins, β-Klotho and γ-Klotho, the latter also known as Klotho/lactase-phlorizin hydrolase-related protein or lactase-like protein. The α-*Klotho* and β-*Klotho* molecules are type I single-pass transmembrane proteins with approximately 1000 amino acids and a degree of 41% amino acid identity. They have a single transmembrane domain and a very short cytoplasmic domain (10 amino acids) without any identified function. In contrast, the large extracellular domain contains two tandem repeats structurally similar to β-glucosidases. Finally, the γ-*Klotho* is a type I single-pass transmembrane protein with a single β-glucosidase-like, extracellular domain and a similarly short intracellular domain [12,13] (Fig. 1). The extremely short cytoplasmic tail makes this domain highly unlikely to perform any signal transduction function.

Tissue-specific expression of Klotho determines the target organs of endocrine FGFs, as most cells express FGFRs [14]. α-Klotho is expressed in the kidney, parathyroid glands and choroid plexus; more recently, its expression in the human vascular wall has been described [15–17]. α-Klotho forms complexes with FGFR1c, FGFR3c and FGFR4 and acts as the high-affinity receptor for FGF23, which in turn induces a common signal transduction pathway [18]. β-Klotho is predominantly expressed in the liver and fat (white adipose tissue), where it forms complexes with FGFR1c and FGFR4. It acts as a cofactor for FGF15/19 (FGF15 is the mouse ortholog of the human FGF19) with FGFR4 as the primary receptor for FGF15/19 signal transduction. In addition, β-Klotho is essential for FGF21 signaling [19–21]. γ-Klotho is expressed in the eye, fat (brown adipose tissue) and kidney, among other tissues, and constitutes a cofactor for FGF19, which subsequently interacts with FGFR1b, FGFR1c, FGFR2c, and FGFR4 [22].

In addition to activating endocrine FGFs by FGF–FGFR–Klotho complexes, Klotho proteins are able to suppress canonical FGF performance, as they compete with different canonical FGF ligands for receptor docking sites [23].

5. Fibroblast growth factors, Klotho and glucose metabolism

FGF19, FGF21 and FGF23 are unique in that they primarily function as endocrine factors that participate in the regulation of important metabolic pathways. FGF19 acts in the postprandial negative feedback regulation of bile acid synthesis and release. FGF21 is a fasting hormone secreted from the liver upon starvation and acts on white adipose tissue. Finally, FGF23 is an essential regulator of mineral metabolism (phosphate and vitamin D). FGF19 and FGF21 are the endocrine FGFs involved in carbohydrate metabolism (Fig. 2).

Experimental studies have shown that intraperitoneal administration of FGF19 increased the metabolic rate accompanied by weight loss but no significant change in food intake [24]. Similarly, transgenic mice with overexpressed FGF19 underwent an increase