Biochimica et Biophysica Acta 1812 (2011) 791–795

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Hormone-like fibroblast growth factors and metabolic regulation

Yun Chau Long, Alexei Kharitonenkov *

Eli Lilly and Company, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285, USA

ARTICLE INFO

Article history:
Received 10 February 2011
Received in revised form 25 March 2011
Accepted 1 April 2011
Available online 12 April 2011

Keywords:
FGF19
FGF21
FGF23
Klotho
βKlotho
Metabolic regulation

ABSTRACT

The family of fibroblast growth factors (FGFs) consisting now of 22 members is generally considered to control a wide range of biological functions such as development, differentiation and survival. However, research during the past decade provided substantial evidence that a so called "hormone-like" subgroup of FGFs, comprised of FGF19, FGF21 and FGF23, is involved in the regulation of diverse metabolic pathways to control glucose, lipid, bile acid, phosphate and vitamin D metabolism. The unique properties of these FGFs include predominant production of the factors in selective tissues, their abundance in the blood due to the lack of extracellular heparin-mediated sequestration, and highly specific tissue-targeted action via engagement of their respective co-receptors. The important metabolic context of FGF19, FGF21, and FGF23 actions has revealed important novel roles for FGFs and provided significant means to explore an opportunity for therapeutic targeting of these factors and their corresponding pathways.

1. Introduction

Energy homeostasis is critical for life; therefore diverse hormonal mechanisms have evolved to regulate cellular energy utilization as well as inter-tissue communication to coordinate metabolic pathways. Although regulation of cellular metabolism by major controllers such as insulin and glucagon is well-established, a new distinct subgroup of fibroblast growth factors consisting of FGF19, FGF21 and FGF23, has been recently identified to play critical roles in the metabolic network. Within FGF superfamily, these three factors share the highest level of homology with one another and propagate their effects via FGFRs, although each of them displays a diverse mechanism of receptor activation. In contrast to classical FGFs that require heparin for efficient FGFR engagement, FGF19, FGF21 and FGF23 lack conventional heparin-binding domains. This property allows these factors to elude body's vast depot of extracellular heparan sulphate proteoglycans and be readily present in the circulation, thus putatively function in an endocrine-like manner [1,2].

Despite the absence of heparin-binding domains, FGF19, FGF21 and FGF23 still require cofactors, type 1 transmembrane proteins Klotho [3] or βKlotho [4], for efficient FGFR activation [5–7]. In contrast to ubiquitously expressed FGFRs, patterns of Klotho and βKlotho expression in the body are fairly restricted. Thus, Klotho and βKlotho, not FGFRs, define tissue selectivity of action for the hormone-like FGFs and determine the distinct physiological roles of these factors: FGF19 regulates cholesterol/bile acid (BA) synthesis, FGF21 controls glucose and lipid metabolism, and FGF23 modulates phosphate/vitamin D metabolism [8–10].

2. FGF19

Transcripts of FGF19 or its mouse ortholog FGF15 are detected in brain, cartilage, skin, retina and gall bladder, but are primarily present in the gut [9,11]. The mechanism of FGFR activation by FGF19 is more complex than other endocrine FGFs. FGF21 and FGF23 do not bind to FGFR directly or function in the absence of their corresponding Klotho cofactors, and their actions are diversely specific toward βKlotho and Klotho, respectively [5,6]. In contrast, FGF19 can directly interact with FGFR4 [12–14], or it may recruit either βKlotho or Klotho as a coreceptor [7,12]. Indeed, in 293 and 3T3-L1 cells that are devoid of endogenous FGFR4, forced expression of βKlotho or Klotho is sufficient to institute FGF19 action [5,12]. Therefore, FGF19 can specifically function in a Klotho independent manner but only via FGFR4, or through multiple FGFRs in the context of Klotho coreceptors expression. FGF19 binds both βKlotho Klotho or via its C-terminus, while N-terminal part of FGF19 is involved in FGFR interaction and activation [13].

The initial evidence that FGF19 regulates body metabolism came from FGF19 transgenic mice. These animals were lean and protected against diet-induced obesity as a result of elevated energy expenditure, enhanced lipid oxidation and increased brown tissue mass [15]. The FGF19 transgenic mice also displayed lower plasma glucose, triglycerides and cholesterol, as well as reductions in the levels of the major metabolic hormones such as insulin, glucagon, leptin and IGF1. The striking metabolic phenotype in FGF19 overexpressing animals can be partly explained by changes in liver gene expression. In the

* Corresponding author. Tel.: +1 3172760091; fax: +1 3172769574.
E-mail address: a.kharch@lilly.com (A. Kharitonenkov).

0925-4439/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbadis.2011.04.002