ELSEVIER

Cytokine & Growth Factor Reviews 16 (2005) 221–232

Cytokine & Growth Factor Reviews

www.elsevier.com/locate/cytogfr

FGF23 and disorders of phosphate homeostasis

Xijie Yu, Kenneth E. White *

Department of Medical and Molecular Genetics, Indiana University School of Medicine, 975 West Walnut St., IB130, Indianapolis, 46202 IN, USA

Available online 5 February 2005

Abstract

It is well known that fibroblast growth factor (FGF) family members are associated with embryonic development and are critical for basic metabolic functions. This review will focus upon fibroblast growth factor-23 (FGF23) and its roles in disorders associated with phosphate handling. The discovery that mutations in FGF23 were responsible for the isolated renal phosphate wasting disorder autosomal dominant hypophosphatemic rickets (ADHR) has ascribed novel functions to the FGF family. FGF23 circulates in the bloodstream, and animal models demonstrate that FGF23 controls phosphate and Vitamin D homeostasis through the regulation of specific renal proteins. The ADHR mutations in FGF23 produce a protein species less susceptible to proteolytic processing. X-linked hypophosphatemic rickets (XLH), tumor-induced osteomalacia (TIO), and fibrous dysplasia of bone (FD) are disorders involving phosphate homeostasis that share phenotypes with ADHR, indicating that FGF23 may be a common denominator for the pathophysiology of these syndromes. Our understanding of FGF23 will help to develop novel therapies for phosphate wasting disorders, as well as for disorders of increased serum phosphate, such as tumoral calcinosis, a rare disorder, and renal failure, a common disorder.

Keywords: FGF; FGF23; Metabolic bone disease; ADHR; TIO; XLH; Fibrous dysplasia; Phosphate wasting

1. Introduction

Maintenance of proper serum phosphate concentrations is required for normal skeletal development and for preservation of bone integrity. In addition, phosphate is required for cellular processes such as energy provision in the form of ATP, is an integral molecule in DNA and RNA, and serves as the substrate for kinase and phosphatase regulation of intracellular signaling. Recent advances in our understanding of disorders involving phosphate metabolism have shed light on the underlying mechanisms that control phosphate homeostasis in normal and in disordered states. This review will focus upon the relationships of fibroblast growth factor-23 (FGF23) to several disorders associated with isolated renal phosphate wasting, including autosomal dominant hypophosphatemic rickets (ADHR), X-linked hypophosphatemic rickets (XLH), tumor-induced osteomalacia (TIO), and fibrous dysplasia (FD). The identification of FGF23 as a possible link for the above syndromes has furthered our understanding of bone and renal phosphate metabolism, and has implications for novel treatment strategies.

1.1. Phosphate homeostasis

Phosphate homeostasis is a complex process involving hormonal regulation at the level of the intestine, kidney, and skeleton. The normal serum concentrations of phosphate are tightly regulated, and in adults range from 2.7 to 4.5 mg/dl, and in children, 4.5–5.5 mg/dl. Most of our current understanding of the control of phosphate comes from the study of Vitamin D and of parathyroid hormone (PTH). In normal individuals, the active form of Vitamin D, 1,25-dihydroxyvitamin D, converted from 25-hydroxyvitamin D by the 25-hydroxyvitamin D1-alpha hydroxylase enzyme (1-alpha hydroxylase) in the kidney proximal tubule regulates serum phosphate concentrations by increasing intestinal calcium and phosphate absorption, and by increasing phosphate mobilization from bone [1]. The subsequent rise in serum calcium concentrations decreases

* Corresponding author. Tel.: +1 317 278 1775; fax: +1 317 274 2387.
E-mail address: kenewhit@iupui.edu (K.E. White).

1359-6101/$ – see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.cytogfr.2005.01.002

PTH secretion, which increases the expression of the primary transport protein in proximal tubule responsible for phosphate reabsorption, the type IIa sodium–phosphate cotransporter (NPT2a) [2]. When delivered in vivo, as well as to cell models in vitro, PTH down regulates NPT2a by decreasing the mean time of the transporter in the apical membrane of the kidney tubule [2].

Phosphate reabsorption in the kidney is measured as the tubular maximum for the reabsorption of phosphorus/liter of glomerular filtrate (TmP/GFR) [3]. Low serum phosphate, or hypophosphatemia, can be secondary to reduced renal reabsorption of phosphate, or a low TmP/GFR. The hypophosphatemia then results in the skeletal defect rickets in children and osteomalacia, a condition of impaired bone mineralization, in adults.

Although much is known regarding the effects of Vitamin D and PTH on mineral metabolism, the study of patients with the rare disorders described herein points to additional, unknown mechanisms involved in phosphate homeostasis. Indeed, these patients have inappropriately normal circulating 1,25-dihydroxyvitamin D concentrations as well as normal PTH concentrations, thus there is a 'disconnect' between phosphate handling and Vitamin D metabolism.

2. Heritable and acquired disorders of isolated renal phosphate wasting

2.1. Autosomal dominant hypophosphatemic rickets

ADHR (OMIM no. 193100) is a rare disorder characterized by laboratory findings of low serum phosphate concentrations due to decreased TmP/GFR [4]. Paradoxically, these patients are also present with inappropriately low or normal circulating Vitamin D concentrations, as well as normal PTH, alkaline phosphatase, and osteocalcin concentrations. Skeletal findings include bone pain, rickets or osteomalacia, fracture, and tooth abscesses [4].

ADHR was first described in a small family [5]. The subsequent study of a large ADHR kindred confirmed autosomal dominant transmission of the disorder, and uncovered that ADHR is characterized by variable penetrance and onset [4]. Patients presented with the disorder in two groups, either as children, with bone pain, weakness, and insufficiency fractures, or as adults, with low TmP/GFR and no extremity deformities. Interestingly, all of the nine adult onset patients described were female, and the onset of disease in some patients presented after pregnancy. Furthermore, two male patients [4], as well as one female patient in an unrelated family [6], who were treated for hypophosphatemia and rickets, lost the phosphate wasting defect. Interestingly, true carriers of ADHR, defined as clinically unaffected individuals having a least one affected sibling and one child, have been observed [4].

To identify the gene for ADHR, the ADHR Consortium undertook a positional cloning strategy. A genome-wide linkage scan in a large ADHR kindred (family 1406) demonstrated significant linkage to a locus on chromosome 12p13.3 [7]. Combined with linkage information from a smaller ADHR kindred (family 1478), this locus was narrowed to a provisional 1.5 MB region for candidate gene assessment. FGF23 was identified using exon prediction programs on chromosome 12p13 genomic DNA sequence from the Human Genome Project [8]. Direct sequencing of FGF23 exons from four ADHR families revealed three missense changes affecting two arginines, which are separated by two amino acids. Families 1406 and 1478 shared the same change in FGF23, R176Q (527G > A). ADHR family 2318 had an R179W (535C > T) change and family 329 had an R179Q (536G > A) substitution [8]. These changes were not found in over 400 control individuals, confirming that the nucleotide substitutions were disease-causing mutations in FGF23. FGF14, which has been identified as the gene for autosomal dominant cerebellar ataxia [9], is the only other FGF family member besides FGF23 to date associated with human mutations.

Several of the FGFs have most likely arisen from gene duplication [10]. FGF23 lies 54 kb telomeric of FGF6, and in a similar manner to the other FGFs, is comprised of three coding exons spanning approximately 11 kb of genomic sequence [8]. The longest human FGF23 mRNA obtained is 3018 bp (GenBank access. no. NM_020638), and contains a predicted open reading frame of 251 amino acids. The 5′-UTR consists of 146 bp with no in-frame stop codon present upstream of the predicted start site. The 3′-UTR consists of 2116 bp with at least one potential polyadenylation signal 831 bp downstream of the stop codon. Prediction analyses also indicated that FGF23 contained a signal peptide, with cleavage most likely occurring between the alanine residue at position 24 and the tyrosine at position 25, a finding confirmed by peptide mapping of recombinant FGF23 [11]. A mouse BAC (BAC No. RP23-195E18) from chromosome 6, within the homologous region to human chromosome 12p13.3 contained the murine homolog of FGF23, that shares 73% identity at the nucleotide level and 70% identity on the amino acid level [12]. Of note, the R residues at positions 176 and 179 mutated in ADHR are completely conserved.

2.2. FGF23 tissue expression

FGF23 is transcribed at low levels in specific tissues. In early studies, hybridization of multiple tissue Northern blots containing control human and mouse RNAs were negative for FGF23 transcripts [8]. In contrast, a Northern blot of cancer cell RNAs displayed a positive signal of approximately 3 and 1.3 kb in the chronic myelogenous leukemia line K562, whereas several other tumor cell lines expressed only the 3.0 or the 1.3 kb transcript. By RT-PCR, FGF23 could be amplified from human heart, liver, thyroid/parathyroid, intestine, and skeletal muscle RNAs [8,13].

In subsequent studies, it has become clear that the tissue with the highest FGF23 expression is bone. Using in situ