Molecular biology of hypophosphataemic rickets and oncogenic osteomalacia

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Abstract  Phosphate plays a central role in many of the basic processes essential to the cell and organism. In particular, skeletal mineralisation is dependent on the appropriate regulation of phosphate in the body, and any disturbances in phosphate homeostasis can have severe repercussions on the integrity of bone. The kidney regulates the serum levels of phosphate by tubular mechanisms which are not fully understood. Furthermore, the processes involved in regulating renal tubular phosphate reabsorption are complex, and involve a large number of factors. It is not surprising therefore that defects in renal phosphate handling result in a failure of bone mineralisation. There are three well characterised conditions which are associated with renal tubulopathies resulting in a phosphate leak, with consequent bone disease. Two are familial, hypophosphataemic rickets (HYP), and hereditary hypophosphataemic rickets with hypercalciuria (HHRH). The third is acquired via a tumour, oncogenic hypophosphataemic osteomalacia (OHO), and may well have relevance to the inherited hypophosphataemias. Recent advances in molecular genetics are permitting the identification of genes involved in human diseases from their chromosomal location. These approaches are now being applied to the analysis of the hypophosphataemias. The isolation of the genes responsible for the renal tubulopathies will be an important achievement. Ultimately this will help to increase our understanding of the mechanisms involved in the control of phosphate handling in the body.

Introduction

The mineralisation of bone depends largely on the availability and appropriate regulation of inorganic phosphate and calcium. The two components form a major part of hydroxyapatite, the mineral part of bone. Since phosphate is integral to the skeletal matrix, depletion of phosphate with abnormally low concentrations in extracellular fluid (hypophosphataemia), causes a failure of mineralisation of the skeleton. This results in rickets in children, or osteomalacia (i.e. softening of the bones) in adults. Rickets in children occurs due to abnormalities during endochondral bone formation at the epiphyseal growth plates, and results in defective bone modelling (bow legs). In addition, remodelling of cancellous bone and apposition of periosteal bone occurs during growth. Defects in mineralisation results in excessive accumulation of osteoid throughout the skeleton. Rickets therefore occurs during growth in children, and osteomalacia presents in adults.

There are a number of well-documented forms of hereditary rickets and osteomalacia that can be broadly classified into two groups. One group of inherited hypophosphataemias occurs due to a changed response to regulation by the hormone 1,25-dihydroxycholecalciferol (1,25 dihydroxy-vitamin-D₃). Two abnormalities have been defined in this group. The first is a failure of the renal 1 o~-hydroxylase, and the second a defect in the 1,25-dihydroxy-vitamin-D₃ receptor (VDR). The second group of hypophosphataemias shows decreased renal tubular phosphate reabsorption as the main abnormality. To date two inherited syndromes from this group have been well characterised, X-linked hypophosphataemic (vitamin D-resistant) rickets (HYP), and hereditary autosomal hypophosphataemic rickets with hypercalciuria (HHRH). Recently other X-linked forms of hereditary rickets have been found (Devoto et al. 1993; Pook et al. 1993), and a family presenting with locus heterogeneity has also been described by Rowe et al. (1992).

This review will confine itself to a discussion of the inherited HYP, and will also refer to the mouse models Hyp and Gy. In addition, a rare acquired form of tumour-associated rickets and osteomalacia, or oncogenic hypophosphataemic osteomalacia (OHO) will be considered. This is because the acquired syndrome has very similar biochemical and radiological features to those of the inherited hypophosphataemic osteomalacias. Thus, it may well serve as a model to help unravel the molecular lesions in the familial X-linked diseases.
X-linked hypophosphataemic rickets

Inheritance

Severe disturbances in bone formation and morphology (rickets), associated with resistance to vitamin D therapy was first documented by Albright et al. in 1937. Winters et al. (1958) recognised that some patients with vitamin D-resistant rickets also had low serum phosphate, and thus classified the syndrome as hypophosphataemic vitamin D-resistant rickets. Originally the disease was described as autosomal (Christensen 1941), and this was because the affection status was determined mainly by observed gross skeletal abnormalities. The finding that some heterozygous females showed no or only mild evidence of skeletal defects but were hypophosphataemic, indicated a non-autosomal inheritance. Using hypophosphataemia as the phenotypic criterion, Winters et al. (1958), Graham et al. (1959) and Burnett et al. (1964) demonstrated that the disease was X-linked with a dominant mode of inheritance. It is the commonest form of inherited rickets with an incidence of 1:20 000 (Burnett et al. 1964). Two mouse models have been described. The first is called Hyp (Eicher et al. 1976), and mirrors almost exactly the human disease. The second is called Gy; in addition to the hypophosphataemia and rickets, the affected mice exhibit a peculiar circling behaviour (Lyon et al. 1986).

Genetic linkage studies

Contemporary molecular genetics using linkage and multilocus analysis first mapped the HYP gene to the short arm of the X chromosome, flanked by two markers (DXS41 and DXS43) 14 cM apart (Read et al. 1986; Machler et al. 1986; Thakker et al. 1987). Considerable refinement of the region has more recently mapped the gene to a smaller interval within Xp22.1–Xp22.2, between two flanking markers DXS365 and DXS1052 (Econs et al. 1993a, b; Rowe et al. 1994). In addition, more genetic information for the RFLP marker, DXS274, which was found to be tightly linked to HYP and also DXS41 with no reported recombinants (Rowe et al. 1992), was obtained by isolating a microsatellite from this locus (Rowe et al. 1993a). Five distinct alleles were detected after screening the HYP families, and a recombinant meiosis against HYP was found in an individual who was previously uninformative for the original DXS274 RFLP. Further genetic mapping has also confirmed that DXS274 is proximal to DXS1052 and distal to DXS41 (Rowe et al. 1994).

More recently, a new microsatellite has been described, DXS1683 (Econs et al. 1994), which was isolated from a cosmid derived from a yeast artificial chromosome (YAC) contig spanning markers DXS365 to DXS41, which flank the disease locus (Francis et al. 1994). Other important contributions to the mapping of the region have been made by Alitalo et al. (1991a, b), who screened retinoschisis and CEPH pedigrees with a number of markers. In addition, Biancalana et al. (1992) have mapped markers tightly linked to the telomeric cluster surrounding DXS43 in studies directed towards the Coffin Lowry gene. The human glycine receptor (HGR) also maps to this region (Econs et al. 1990). The combined genetic map is shown in Fig. 1, and of particular interest is the large cluster of medically important genes mapping to this region. The genetic map of the area has also been further refined with particular reference to Coffin Lowry (CLS) and retinoschisis (RS) genes (Biancalana et al. 1994), and an additional marker tightly linked to DXS365 has been described, DXS1229. The most likely locus order and map distances were: Xpter-DXS16-(3.4)-(DXS207, DXS43, DXS1052)-DXS1229-DXS1683-DXS41.