The Role of PEDF in Bone Mineralization

F. Rauch

Shriners Hospital for Children — Canada, 1529 Cedar Avenue, room 300, Montreal, Quebec, Canada

BACKGROUND: Osteogenesis imperfecta (OI) type VI is a heritable disease that leads to a large number of fractures in children. It is caused by genetic mutations that lead to the absence of pigment-epithelium derived factor (PEDF) in all body cells. PEDF is a protein that is produced and secreted by cells in many tissues (liver, eye, fat). In bone, it is particularly highly expressed in osteoblasts, the bone-forming cells. The function of PEDF in these cells is not known at present. It is clear, however, that PEDF deficiency results in OI type VI.

Osteoblasts secrete organic bone matrix, which to a large extent consists of collagen type I. Once the organic matrix is deposited in the extracellular space, it needs to 'mature' in order to accommodate mineralization. After a lag time of about 2 weeks, the mineralization process starts, i.e., mineral (mostly calcium and phosphate) is deposited in the organic bone matrix. This process can be examined by analyzing bone tissue samples from patients and comparing the results to those of people who do not have a bone disease. Using bone tissue samples, the mineralization process can be described by a number of measures: the amount of unmineralized organic bone matrix (osteoid); the duration of the lag time between the deposition of organic matrix and the start of mineralization ('mineralization lag time'); the average density of the mineralized bone (percent calcium content, representing the percent of the mass contributed by calcium).

OI type VI is associated with a unique set of findings in the measures reflecting bone mineralization. On the one hand, the start of mineralization is delayed. This is reflected by a prolonged mineralization lag time, and an increase in the amount of unmineralized osteoid. On the other hand, the mineralized part of the bone tissue is 'hypermineralized'. This is reflected by a very high percentage of calcium content. It thus appears that absence of PEDF has two different effects on bone mineralization. First, the start of the mineralization process is delayed. Second, once mineral starts to be incorporated into the tissue, the mineralization overshoots and incorporates more mineral into the organic matrix than in normal bone (increased 'material bone density'). This 'hypermineralization' may explain the extreme brittleness of the bone in children with OI type VI.

The relationship between PEDF and bone mineralization has not been studied. It is therefore not known which aspect of the mineralization process (collagen secretion, collagen 'maturation', other proteins interacting with the mineral in the organic matrix) is affected by the absence of PEDF.

QUESTION: Can the action of PEDF on the bone mineralization process be modelled to identify the putative function of PEDF in the mineralization process? Such a model would help to identify the interaction partners of PEDF during the mineralization process.

LITERATURE

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