Effects of Calcitriol on the Biogenesis of a Lysosomal Protease in Monocytes from Patients with Renal Failure

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Dear Sir,

The principal resorbing cell of bone, the osteoclast, originates by fusion of circulating mononuclear precursor cells and represents one of the end stage cells of mononuclear phagocyte differentiation. Osteoclasts excavate mineralized bone matrix by tightly adhering to it and by isolating a subosteoclastic microenvironment wherein very low pH values can be generated and hydrolases are released. Degradation of bone collagen follows, owing the combined action of collagenases and lysosomal proteinases. Among the latter, cathepsin D(CD) is primarily responsible for the degradation of the organic matrix of skeletal tissues [1].

Like osteoclasts, monocytes and macro-phages possess the capacity to attach to and degrade bone matrix and serve as a model to study the mechanisms of bone resorption in tissue culture [2]. 1,25-Dihydroxyvitamin D₃ is known to increase number and size of osteoclasts [3] and induce the expression, synthesis and secretion of CD in U937 promonocytes [4].

We examined the influence of calcitriol (100 nmol) on biogenesis and secretion of CD in cultured monocytes from patients in advanced renal failure (serum creatinine values ranging between 590 and 707 $\mu\text{mol/l}$) using established metabolical labelling and immunoprecipitation techniques [5].

In monocytes from 10 normal subjects calcitriol enhances maturation of CD, as compared to the pattern from control (i.e. unstimulated) cell suspension. Compared to normal, a relative increase in extracellular secretion of both mature enzyme (from lysosomes) as well pro-CD(from Golgi apparatus) was observed in 10 sex- and age-matched uremic patients. 1,25-Dihydroxyvitamin D enhances the maturation process of CD, thus partially reversing the abnormal transport of the protease in patient monocytes.

The lysosomal system probably plays a key part in the resorption of articular and connective tissue both in physiological remodelling and during pathological damage [6]. Locally elevated concentration of H⁺ and Ca²⁺, as well as a cooperation between lysosomal cathepsins and collagenase, play an important role in the breakdown of collagen that is carried out by the osteoclast in a specialized bone-resorbing microenvironment. Our in vitro experiments, using monocytes as a model of study of the effects of calcitriol on potential bone resorptive cells,

indicate that cultured monocytes from uremic patients display an abnormality in the transport of lysosomal enzyme CD from Golgi apparatus to prelysosomal vesicles and eventually lysosomes, and that the exposure of cells to calcitriol partially restores the impaired biogenesis of CD in patient cells.

Calcitriol-treated monocytes produce increased amounts of interleukin 1, tumor necrosis factor and prostaglandin 2, all of which induce bone resorption, and block production of interferon- γ [7], which can inhibit calcium mobilization from bone, the net effect of calcitriol activity, therefore, favors bone resorption and increases calcium mobilization [7]. Beside these effects one must now consider the regulation of the synthesis and secretion of critical lysosomal enzymes.

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