BONE

Recessive osteogenesis imperfecta and cyclophilin B

The genetic etiology of recessive osteogenesis imperfecta, which accounts for 5–7% of cases in North America, is a deficiency of components of the collagen 3-hydroxylation complex. The three components of the complex are prolyl 3-hydroxylase 1 (P3H1), cartilage-associated protein (CRTAP) and cyclophilin B (CyPB). In type I collagen, the substrate of the complex is the α1(I)Pro986 residue.

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In previous studies, the group of Joan C. Marini (National Institute of Child Health and Human Development, Bethesda, MD) studied a cohort of patients with osteogenesis imperfecta with rhizomelia (shortening of proximal segments of upper and lower limbs), whose collagen was overmodified similar to dominant osteogenesis imperfecta, but who did not have collagen defects. The investigators demonstrated that these patients had null mutations in either *CRTAP* or *LEPRE1*, the gene that encodes P3H1. All patients had reduced 3-hydroxylation of the collagen α1(I)Pro986 residue.

In a follow-up study published in the *New England Journal of Medicine*, Barnes *et al.* report on two siblings studied by the Marini group in collaboration with Cathleen Raggio (Hospital for Special Surgery, New York). The probands have recessive osteogenesis imperfecta without rhizomelia, owing to a homozygous mutation in the start-codon of the peptidyl-prolyl isomerase B gene (*PPIB*), which results in the lack of CyPB.

“Because CyPB has been thought to be the rate-limiting peptidyl-prolyl cis-trans isomerase for type I collagen, we examined the effect of absence of CyPB on collagen folding using gel electrophoresis of steady-state collagen, mass spectrometry and differential scanning calorimetry, all of which supported the conclusion that collagen folded at a normal rate in these cells,” explains Marini.

Clinically, the most crucial finding was that these siblings had moderate osteogenesis imperfecta without rhizomelia, instead of the severe, lethal osteogenesis imperfecta with rhizomelia seen with null mutations in either of the other components of the complex, CRTAP or P3H1. Biochemically, the surprising findings were that the collagen showed normal folding and normal helical modification, as well as normal 3-hydroxylation of the α1(I)Pro986 residue.

“Future experiments will reflect our interests in collagen and bone,” says Marini. “We are interested in the effect of the absence of the complex on collagen folding, trafficking and secretion from the cells.”

The question remains whether the hydroxylation of α1(I)Pro986, the binding of the complex to collagen or the chaperone activity of the complex is crucial for collagen folding. It would also be interesting to compare the effects of the absence of CyPB to the presence of defective CyPB protein.

Although these studies will not immediately affect the treatment of osteogenesis imperfecta, the delineation of these pathways will hopefully reveal novel targets for drug therapies.

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Original article Barnes, A. M. *et al.* Lack of cyclophilin B in osteogenesis imperfecta with normal collagen folding. *N. Engl. J. Med.* **362**, 521–528 (2010)