A new receptor to turn on bone growth

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NZ Med J 2002; 115: 169-70

Several years ago, an eleven year old child was referred to the Bone Clinic at Auckland Hospital with a history of multiple vertebral fractures occurring after minimal trauma. She also had severe visual impairment. Her care was taken over by Dr Tim Cundy who specialises in paediatric bone disease. He recognised her as fitting the diagnostic criteria for osteoporosis pseudoglioma syndrome, a congenital condition of unknown cause and with no known treatment – a depressingly common combination of circumstances in the field of paediatric bone disease. Tim established contact with a group at Case Western Reserve University in Cleveland led by Dr Matt Warman, who were attempting to identify the genetic lesion responsible for this autosomal recessive condition. Accordingly, clinical data and DNA were contributed from the Auckland patient and her family. Another New Zealand patient and his family also took part, and two families from Australia were recruited to the international group, which included collaborators from fifteen countries.

This major international collaboration has now borne substantial fruit. In a paper recently published in Cell,1 they reported that the gene causing osteoporosis pseudoglioma syndrome is that for the LRP5 receptor, a member of the low density lipoprotein receptor family. These receptors do not seem to be involved in lipid metabolism, and they have never previously been known to have any involvement in bone development. However, they are expressed in osteoblasts and appear to regulate osteoblast proliferation and/or differentiation. Interestingly, individuals who are heterozygous for the abnormal gene (such as the parents) do have a substantially reduced bone density, though they do not have the major problem with fracturing which the homozygotes have. This implies that even a single copy of the abnormal gene has a significant impact on normal osteoblast function.

While this programme was proceeding in a number of centres around the world, a similar clinical genetic study was being carried out completely independently in Omaha, Nebraska. Dr Robert Recker and coworkers had identified a large family with very high bone density and had set about identifying the genetic variant that accounted for this phenomenon. At almost the same time as the data from the osteoporosis pseudoglioma group was presented, Recker's group reported that the family they were studying had an activating mutation of the gene for the LRP5 receptor, providing confirmation of the pivotal role that this receptor plays in osteoblast biology. Again, this group's work demonstrates the enormous synergies that result from astute clinicians working hand in hand with molecular biologists.

The product of these collaborations provides many questions for bone biologists to address. What are the endogenous ligands for the LRP5 receptor, which aspects of osteoblast function are regulated by it, and how does it interact with the other well recognised osteoblast regulators such as parathyroid hormone and calcitriol? This work will also open up enormous new horizons to pharmacologists who now have a novel receptor target at which they can aim new therapeutic agents for the management of osteoporosis. This is especially welcome at a time when almost all available pharmacological agents for managing this burgeoning clinical condition act by inhibiting the activity of the bone resorbing cells, the osteoclasts. To have discovered a switch which will turn on bone formation represents an enormous leap forward in the quest for a pharmaceutical which is truly a bone “anabolic”.

So does this sophisticated research have any relevance to the average practising clinician? I would suggest that it does in at least two quite different ways. The major discoveries made by the two groups outlined above, were entirely dependent on observations made by practising clinicians, some in small centres, who had the enterprise and initiative to form collaborations so that the DNA on which both these discoveries depended, could be collected. We should be mindful of this in
all our clinical work, particularly when dealing with patients with conditions of unknown aetiology. The current state of investigations into the genetic aetiology of such conditions can be accessed using the Online Mendelian Inheritance in Man website (access by searching OMIM). The second point of impact of this work on clinical practice will arise from the major novel insights into osteoblast biology which will result from this work. These may result in novel diagnostic tests or they may result in new pharmaceuticals, as discussed above. Either development has the potential to substantially affect the lives of osteoporosis sufferers and to impact on the epidemiology and economics of this major public health problem.

While these developments are novel and exciting in 2002, in 5-10 years’ time they will be being taught to medical students and have the same status as the currently established elements of bone biology. The exciting fact of practising medicine in an era of such investigative sophistication is that we are constantly confronted by new discoveries, carrying with them the possibility of novel therapeutic interventions. This increases the challenge involved in the practice of medicine but it also greatly increases the fulfilment of our professional lives since we see long-standing puzzles being solved, and enjoy the satisfaction of being able to offer our patients new treatments for previously intractable conditions.

**Acknowledgement.** I am grateful to Assoc Prof Tim Cundy for help in preparing this article.

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