Bones, muscle, medals and privacy

This column has often dealt in developmental matters, mainly since it becomes clear, in the authors view, that much of our susceptibility to degenerative disease depends on how we are put together initially. But it is not only degeneration; a natural myostatin-inhibiting mutation has produced a European weightlifting champion, as well as the Belgian Blue cattle and a family of ‘long-distance’ champions—the Mantyrantas, with a double Olympic cross-country skiing gold medalist in their number, have a mutation that results in an increased response to normal production of erythropoietin. More recently, as techniques and information handling get better, it has been possible to show that elite sprinters have more than one copy of a form of \textit{ACTN3} that is associated with ‘fast’ fibre production (20% of us lack it completely: that’s why you came last in the Mothers or Fathers race this summer). Around 90 genes have been identified that affect athletic performance, and gene doping is already discussed in relevant publications. The Tour de France is a potential field of interest to me; did you know that of all major athletes, those who finish the Tour are alone in having a reduced life expectancy when compared with the rest of their native populations? (There are some notable confounders in that, however).

So in the process of forming our bones, are we all as variable? There is no reason to suppose not, and the process is so multi-stepped that it seems likely to be so. How might osteoporosis depend on how you make bones?

The osteoblastic bit is easy. Endochondrial ossification, a well-defined process, predominates in the mammalian skeleton. A mesenchymal condensation forms where a bone will be, expressing bone morphogenetic receptor IB (BmpRIB) and, as differentiation begins, type II collagen. Around each condensation, a thin spindle-celled perichondrium differentiates and inhibits the proliferation and maturation of chondrocytes [Bmp 7 and parathyroid hormone/parathyroid hormone-related peptide receptor (PTH/PTHrP) receptor are expressed]. The cartilaginous precursor of the bone is clearly divided into zones—a rapidly proliferating zone is succeeded by a zone where cells are separated by a stroma; these are pre-hypertrophic chondrocytes [expressing sonic hedgehog (Shh), Indian hedgehog (Ihh) and BmpRIB] and a zone of hypertrophic cells. Ossification occurs as chondrocytes cease dividing, produce abundant matrix (type IX collagen is produced), and become hypertrophic with accompanying vascularization of the anlage and invasion of bone-forming cells (osteoblasts). This process begins in the centre of the bone and spreads towards the ends, where it stops short of the growth plate.

\textit{Ihh} inhibits chondrocyte differentiation and prevents maturation and ossification—the growth plate does not express \textit{patched} or \textit{Gli}, which are necessary as receptors for \textit{Ihh}. Targeted disruption of the \textit{Ihh} gene results in short-limbed dwarfism.

The destruction of bone in modelling and turnover is, of course, a function of the osteoclast. The osteoclast is a member of the monocyte/macrophage family and is characterized by polarization—it has an altered surface, induced by contact with bone, just as epithelial cells are polarized in terms of their contacts with basement membranes. The main peculiarity of the cell is its resorptive organelle, the ruffled membrane, formed in contact with bone and comprising a villous-like complex of the plasma membrane that contains numerous vacuolar proton pumps (H\textsuperscript{+}ATPases). Increased activity of individual osteoclasts or an overall increase in number can cause osteoporosis; less commonly, localized lesions (Pagets disease of bone, or hereditary expansile polyostotic osteolytic dysplasia, HEPOD) are caused by osteoclast gain of function. Failure of osteoclastic activity leads to osteopetrosis, and this occurs in a number of forms. The autosomal recessive ‘malignant’ osteosclerosis is a failure of osteoclast stem line differentiation; in the so-called benign forms (usually autosomal dominant but occasionally recessive), osteoclast function is defective. These failures may be due to failure of osteoclasts themselves or in the cells that support osteoclast precursor differentiation.
There are probably a hundred or so genes that might confer advantage/disadvantage in the process and result in a skeleton that is fracture-resistant in old age. There are models of osteogenesis imperfecta in animals, produced by genetic manipulation, and in one strain (Brittle IV), adaptations that improve bone strength have been studied. Gene therapy has been used in this disease, but its heterogeneity makes this difficult, and a direct assault on skeletal formation may be less effective than controls on turnover. So should we look for a typing system that helps us to predict who is at risk and only treat them? (I am firmly convinced that population-based advice, whether to do with lipids, alcohol, fatty fish, anti-oxidants or exercise is counterproductive—even more so is prophylactic therapy). The difficulty of such a specific scheme is evident, and a major difficulty can be envisaged.

Unrelated individuals differ in about 0.1% of their 3.2 billion genome bases. Forensic identifications depend on around 13–15 locations of variable repeats, and single nucleotide polymorphisms (SNPs) can be used to identify individuals. Small sets of SNPs can allow the identification of individuals if there is access to the DNA database, and if there are $10^{10}$ people in the world, specifying sequences at 30–80 independent SNP positions will define an individual. In practise, those who are inquisitive would need much less in the way of genetic information (if an SNP is relatively rare, the numbers become remarkably small). If there is kinship data, a few positions are all that is needed. It has been suggested that deliberate random changes introduced into the data on anything ‘published’ would help in maintaining anonymity, but 75 SNPs would confound that in every case where 10% of the bases had been fiddled. It seems that there will have to be control of access to the database if this difficulty is seen as a real problem—there are enough genes involved in the clinical entity of osteoporosis to make it a reasonable case study of the issue—when we know what to look for!

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