Immune System and Bone Regeneration

At the recent three-day International Symposium on Bone Regeneration in Berlin, basic and clinical scientists presented their latest research on the complex interplay between the immune system, progenitor cells and cell-matrix interactions, all of which are involved in bone regeneration. To keep track of the critical points made by the 12 keynote speakers, a highly talented graphical illustrator worked continuously throughout the symposium producing cartoon drawings, illustrating the various threads that interconnected to make a wonderfully colourful montage depicting bone regeneration. This proved to be a uniquely powerful reference tool for all the participants, facilitating a greater understanding of the complex interconnecting processes of bone regeneration.

Bone is a very special tissue in that repair, remodelling and regeneration occur by formation of tissue that replicates the original tissue, without formation of scar tissue as in most other organs. Failure or inadequate bone regeneration in fractured bone, resulting in delayed or non-union is a vexing clinical problem in all species of animals. Recently, the focus of attention in orthopaedics has been on the treatment of fractures by bone grafts, mesenchymal stem cells, growth factors, biomaterials and improved mechanical environment, either alone or in some combination. These therapies have produced clearly demonstrable benefits in treating delayed and non-union. However there is still much to learn about the complex processes of fracture healing, and why it fails in some patients despite the management by ‘state of the art’ surgery employing, for example, minimally invasive osteosynthesis, locking implants, exogenous growth factor application, and 3D printed biomaterials and stem cells for the reconstruction of critical sized defects. Even so, in a proportion of fracture patients, endogenous factors predispose to impaired fracture healing.

The pivotal role of immunity in fracture healing and bone regeneration was one such endogenous factor under discussion at the symposium. The immune system has direct involvement in guiding all stages of fracture healing starting with inflam-

http://dx.doi.org/10.3415/VCOT-15-06-0105
mation, progressing with repair, and finishing with remodelling. Recently it has been shown that adaptive acquired immunity has an important effect in murine models of fracture healing as well as in human patients with proximal tibial fractures repaired with internal fixation (1). Human patients with elevated numbers of CD8+ T cells in their peripheral circulation at the time that they sustain a fracture, have an increased risk for developing a delayed union. This is because the CD8+ T cells migrate into the fracture haematoma and produce interferon-gamma and tumour necrosis factor alpha, which inhibit osteogenic differentiation and survival of human mesenchymal stromal cells. This blocks osteogenesis, causing delayed union. Experimentally it was found that blocking the CD8+ T cells in the murine fracture model allowed normal fracture healing. These studies highlight the importance of innate susceptibility of some patients to non-union. They also go some way to explaining why delayed and non-union are reported to be a complication in 5–20% of fractures and osteotomies, in spite of employment of best practice treatments.

Some other examples illustrating the critical involvement of the immune system in bone regeneration are the following. The predominant effects of mesenchymal stem cell therapy are probably not due to stem cell differentiation to functional osteoblasts and chondroblasts per se, but rather activation of macrophages as well as trophic action on region host cells. As another example, the intermittent administration of parathyroid hormone has an anabolic effect on the skeleton, increasing bone mass. This occurs due to the direct action of parathyroid hormone on T cells, which in turn stimulate osteoblast differentiation and bone formation via Wnt signalling. These are just two examples illustrating the involvement of the immune system in bone regeneration.

I came away from this symposium optimistic that the incremental accumulation of knowledge about the complex process of bone regeneration will hopefully result in a better understanding of how we can improve our treatment of fracture patients in the future.

References