osteogenesis is clear, but osteoclasts are required for the remodeling at later stages to produce bone deposition or resorption. The requirement for greater osteoblast activity during activity is achieved by Osteoprotegerin (OPG), released by osteoblasts, which prevents RANKL osteoblasts and osteoclasts. Bone resorption is achieved by attachment of the osteoclast to proteins such as osteocalcin and osteonectin. Osteoid is then mineralized by the osteoblast through calcium hydroxyapatite deposition.15 Inhibition of osteoblast activity is through a number of molecules such as Neogenin, SOST and NKX3. These processes are illustrated above.

Osteoblast development

Corticotomy

Distraction Osteogenesis in Practice

Distraction osteogenesis requires a fix to the bone segments and control their position. This is achieved using an external frame such as the Ilizarov, or an intramedullary nail. Distraction osteogenesis is used in two ways: for bony transport to fill large defects, achieved by corticotomy of bone at the opposite end to the defect, and moving the resulting bone segment into the defect. As the bone segment is pulled down, the widening corticotomy is filled with new bone. The process involves 3 phases.

Distraction Osteogenesis - Late Phase

There is no bone movement in this phase. The healing process begins in surgery, with an immediate response similar to that seen in any other injury. This involves high levels of pro-inflammatory cytokines, growth factors, prostaglandins and angiogenic factors. Some of these, such as IL-1, IL-6 and BMPs begin to recruit and drive MSCs into osteoblasts. Angiogenic factors such as VEGF initiate local angiogenesis, one of the most important processes in the late phase. Over several days the inflammatory factors subside, and the next phase begins.

Distraction Osteogenesis - Consolidation Phase

In the consolidation phase separation of bone sections is halted, and tension on the new bone falls as the segments adjust. This allows consolidation of the new bone, a process of bone maturation, called reshaping and reestablishment of the bone cortex as seen in the left X-ray.

This phase is characterized by levels of signaling molecules. The other particularly important levels of BMP-3 however rise in this phase, reflecting a suggested role in bone remodeling. Similarly, with fewer osteoblasts present levels of RANKL and OPG fall, so osteoclast activity becomes less extensive with time, and reaching a normal osteocalcium requirement.

Angiogenic factors and other growth factors also fall, unsurprising given the peak vasculature is present. Levels of IL-6 also fall as tension decreases. Ultimately, after a period of time (41 weeks in this case), the defect is filled with new bone with the same mechanical properties as native bone, and the framework can be removed, as can be seen in the X-ray on the right.

Future Directions

There are 3 basic processes that can be manipulated to improve distraction osteogenesis.

- **Inhibition of osteoclasts.** Case series have shown that bisphosphonate use during distraction can improve outcome in examples of insufficient regeneration or poor bone union. Other possible inhibitors of osteoclast function are used. The drive to produce these factors is believed to be the consequence of hypoxia or hypoxia induced factor 1 alpha (HIF-1α).

- **Stimulating osteoblasts.** Parathyroid hormone (PTH) increases bone mass if given intermittently and is in use clinically for cases of poor regeneration. Recombinant BMP-2 and 7 are FDA approved for use in open fractures and spine fusion; multcentres experiences have shown them to be safe and to improve healing outcomes. While not licensed for distraction osteogenesis, it is likely this will happen with greater experience and trials.

- **Enhancing angiogenesis.** With such dependence on a robust vascular supply in distraction osteogenesis, the use of growth factors and cytokines to increase angiogenesis may speed healing or allow an increased distraction rate. There are dangers involved in stimulating cell proliferation systemically, but local administration may be an option.

Conclusion

Distraction osteogenesis is an orthopaedic surgical procedure used in the correction of complex fractures, previous fracture repair complications, and bony deformities. Success depends on the controlled separation of bone segments over time inducing vigorous bone regeneration in a surgically introduced gap. This process is affected by an array of factors and their effects at the molecular and cellular levels. With increased understanding of distraction osteogenesis biology, new treatments are being developed to improve healing. This will have impacts not just on distraction osteogenesis, but other bone pathologies as well.

References