Introduction

Our skeletons provide the foundations on which our bodies are built, providing both mechanical support, protection of soft tissues, and a role in mineral homeostasis and haematopoiesis. Rather than being static and unchanging, our bones are constantly being torn down and rebuilt at a cellular level, a process termed remodeling. This serves to repair microtrauma as it occurs, strengthen areas of greatest stress, and to prevent the build up of aged bone. So great is this remodeling, that our skeletons are never more than ten years old or so.1 The cells responsible for remodeling are also involved in repair, and so great are their abilities that the resulting bone is virtually indistinguishable from native bone,2 in comparison to the repair of other body tissues with the laying down of scar tissue.

In some cases fracture repair is unsuccessful, due to factors such as infection, poor vascular supply, or simply a severe enough defect, resulting in a non-union. Surgical repair of such difficult fractures was revolutionized by Gavriil Ilizarov during the 50s, who, when expanded on earlier techniques3–5 involving the controlled separation of bone pieces to induce bone growth in the resultant gap - this is 'distraction osteogenesis'.6 Ilizarov produced an external frame to allow fine control of bone movement in distraction osteogenesis over extended periods of time (months). This technique allows repair of bone deformities and complicated fractures, but is dependent on the reparative capacities of our bones.

Build It Up, Tear It Down

The major cells responsible for bone growth and resorption are osteoblasts and osteoclasts. Osteoblasts are largely derived from mesenchymal stem cells (MSCs), which are driven down the osteoblast differentiation pathway by specific signaling molecules such as Indian hedgehog (Ihh) and Bone Morphogenetic Proteins (BMPs). These drive the expression of genes that produce a mature osteoblast able to respond to stimulatory signals to produce bone. Osteoclasts achieve this by secreting osteoclast, a matrix consisting of cross-linked collagen fibrils with added proteins such as osteocalcin and osteonectin. Osteoid is then mineralized by the osteoblasts through calcium hydroxyapatite deposition.7 The inhibition of osteoblast activity is through a number of molecules such as Noggin, SOST and NKK. These processes are illustrated above.

Osteoblast development

Osteoblasts are capable of strong RANKL production, providing a coupling step between driven down the osteoclast pathway by two major signaling molecules, M-CSF and RANKL.8 These cells are derived from the same haematopoietic stem cell pool as macrophages, and are functional opposites to osteoblasts, being responsible for bone resorption.9

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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 nailing. Distraction osteogenesis is used in two ways:10

1. Prolonged positive effect on osteoblast function:10

- Similarity, levels of many BMPs rise during the distraction phase, promoting osteoblast maturation and laying down of new bone.11

- The rising osteoblast population promotes osteoblast activity by strong RANKL signaling. As osteoclasts move cartilage tissue laid down during the distraction phase to allow intramembranous ossification to take place, they promote osteoblast activity, allowing bone formation to outstrip bone resorption. To support such a drive, osteoclast resorption is essential.

- High level of cellular activity, a good example of distraction osteogenesis is produced through the action of VEGF and angiopoietins, which are found to be expressed in high levels during bone regeneration.12

- The drive to produce these factors is believed to be a combination of stress tension, weight bearing, and hypoxia, given the up regulation of hypoxia inducible factor (HIF) 1 α and 2 α.13

- The angiogenic drive is so great that the entire limb is affected.14

- An important factor in distraction is the rate at which the bone segments move. Too slowly and premature consolidation occurs, resulting in microfractures. Too high a distraction rate and bone formation is poor, with the defect being filled with fibrous tissue and areas of hemorrhage and necrosis.15

- The act of separating the bone sections promotes efficient remodeling, that our skeletons are never more than ten years old or so.16

Distraction Osteogenesis - Consolation 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, calls reshaping and reestablishment of the bone cortex as seen in the left X-ray.

This process is reflected by levels of signaling molecules. The levels of BMP-3 however rise in this phase, reflecting a suggested role in bone remodeling. Similarly, with fewer osteoclasts present levels of RANKL and OPG fall, some angiogenic factors less extensive with time, and reaching a normal osteoclast requirement.

A 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 possibilities include OPG mimics to inhibit osteoclast maturation and activation, and inhibitors of mature osteoclast function e.g. enzyme and protein pump inhibitors.

- Stimulating osteoblasts. Parathyroid hormone (PTH) increases bone mass if given intermittently and is in use clinically for cases of poor regeneration.17 Recombinant BMP-2 and 7 are FDA approved for use in open fractures and spine fusion; multicentre experiences have shown them to be safe and to improve healing outcome.18 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 systematically, 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 bone 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.

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References

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