The Biology of Fracture Healing in Long Bones

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139.4 Abstract

The healing of a fracture is one of the most remarkable of all the repair processes in the body since it results, not in a scar, but in the actual reconstitution of the injured tissue in something very like its original form. It is not to be expected therefore that the mechanisms controlling such a process will be easily elucidated and indeed they involve problems of cellular homeostasis, which are among the most fundamental in biology. If it is not quite the "cunning' pattern of excelling nature" then it is something quite close to it and a great deal of that pattern at present stands unrevealed.

However, this review is primarily concerned with those features, which have direct clinical relevance, and it is fortunately possible to treat fractures successfully without a complete understanding of the cellular mechanisms involved without at the same time relying entirely on empiricism. A number of factors influence the healing which can be identified from both clinical and experimental work and may be taken into consideration to put treatment on a more rational basis.

It is with these observations that we shall be particularly concerned and cellular mechanisms will be discussed only if they appear to have clinical implications. Such an account must necessarily include details of the healing process as it is modified by contemporary methods of treatment but first it is necessary to consider the events that occur in the healing of a simple fracture in an unsplinted long bone.

139.5 Summary

Fracture healing involves two processes: one is direct or primary healing, and the other is indirect or secondary healing.

Primary healing consists of cutting cones (tunnelling osteoclasts followed by osteoblasts forming new bone) which progress across the fracture site directly in a similar way to normal bone remodelling. The process involves intramembranous bone formation and direct cortical remodelling with or no periosteal response (no callous formation).

Primary healing occurs in cases of anatomical reduction, extreme stability and negligible gap size, involving a direct attempt by the bone to form itself directly.

In secondary or indirect bone healing, an external callus is formed which serves as a splint that stabilizes the fracture fragments. New bone formation in the external callus occurs via both intramembranous and endochondral ossification. It is generally enhanced by motion and inhibited by rigid fixation.

The fracture of a long bone triggers a cascade of events. After the initial hemorrhage and release of thrombotic factors, tissue breakdown releases mediators that modulate the migration of blood cells and mesenchymal cells [1]. Cytokines and growth factors are released both locally and systemically and induce a mitogenic and osteogenic effect on the osteoprogenitor cells. The formation of new blood vessels, in

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association with further growth factor and prostaglandin production, promotes differentiation of mesenchymal stem cells (MSCs) toward chondrogenic or osteogenic lineages, forming initially woven bone and in turn, the hard callus.

Numerous adverse mechanical and biological factors influence the development of nonunion: excess motion, a large interfragmentary gap, loss of blood supply, severe periosteal and soft tissue trauma.

The process of bone replacement and repair are going on continuously in the normal skeleton and the mechanisms involved in fracture healing are no different.

139.6 Citations

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139.7 Related References

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139.8 Key Message

Bone healing is one of the most complex cascades of events aiming to the repair of fractured bone without the formation of scar tissue. The majority of fractures unite by secondary bone healing. This progresses in five stages, as described by McKibbin, namely haematoma formation, inflammation, formation of soft and then hard callus and finally remodelling.

139.9 Why Is It Important

This is a classic orthopaedic article in which McKibbon describes the biology of long bone repair. Despite ongoing advances in orthopedics to enhance bone healing, about 5–10 % of fractures still develop delayed union or nonunion [2].

139.10 Strengths

This was a comprehensive review article outlining various mechanisms and theories of fracture healing.

139.11 Weaknesses

McKibbin suggested that the contribution of the bone marrow to the healing of a fracture might be minimal, the study of Brighton and Hunt [3] provided evidence that the bone marrow makes a direct contribution to the formation of bone during the early phase of healing.

139.12 Relevance

Before 1965, most researchers viewed the osteoblast as the key cell of bone healing and any problems associated with bone healing. Studies at the time reflected issues of how existing osteoblasts responded to drugs, hormones and systematic disease. In 1965, Urist revolutionised the current under- standing of fracture healing by hypothesising the existence of bone morphogenetic proteins (BMPs) allocated onto the extracellular collagenous matrix.

By the mid 1970s the biology of fracture healing began to be more fully understood as a complicated process in which a series of cellular and molecular events leads to structural reconstitution and tissue regeneration. Secondary bone healing has been characterized by four overlapping phases: an inflammatory phase, a soft callus phase, a hard callus phase, and a remodelling phase.

139.12.1 Inflammatory Phase

Trauma causes bleeding that disrupts the fracture site, periosteum and surrounding soft tissues and results in the formation of haematoma. The haematoma forms an important source of haematopoietic cells and platelets that initiate the inflammatory process. The haematoma releases a large number of signalling molecules, including cytokines and growth factors.

Cell division is first seen in the periosteum and to begin with extends the length of the injured bone. Within a few days this activity is confined to the immediate area adjacent to the fracture where it remains above normal levels for several weeks.

The ends of the broken bones do not appear to participate in the initial reaction, and are in fact dead as evidenced by the empty osteocyte lacunae, which extend for a variable distance from the fracture.

139.12.2 Soft Callus

Soft callus formation occurs by endochondral ossification at and overlying the fracture area. The amount of cartilage is

variable, occurring prominently in lower animals and where excessive movement is permitted.

139.12.3 Hard Callus

McKibbin suggested from his observations that hard callus formation is part of the initial inflammatory response to fracture and is predominantly driven by biological factors.

139.12.4 Remodelling

Woven bone is remodelled into stronger lamellar bone by the orchestrated action of osteoclast bone resorption and osteoblast bone formation.

Mckibbin suggest local inflammation initiated bone regeneration by stimulating the migration of mesenchymal stem cells, fibroblasts, and endothelial cells, as well as immune cells such as macrophages, driving the formation of soft callus and further processes.

McKibbin also emphasized the relationship between the different types of calluses and their mechanical properties For McKibbin; one of the most important functions of the endosteal callus is to take a part in the stabilization of the fracture gap by settling the fracture gap with immature bone. Osteocytes located at the fracture ends become deficient in nutrients and die, which is observed by the presence of empty lacunae extending for some distance away from the fracture.

References

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