Introduction: The Rationale for Understanding the Biology of Injury

Bone and cartilage healing are central to the practice of orthopedic surgery. Orthopaedic treatments should attempt to optimize the cells, scaffold, molecules, and blood supply required for healing. This chapter will describe the components required for successful healing, detail the role of each factor, and outline the complex interactions that occur during the healing processes of bone and cartilage. The cellular processes of bone and cartilage healing will also be examined in detail with a focus on the dynamic repair processes, and the disruptions that impair successful healing particularly as it relates to factors under a surgeon’s control.

The clinical importance for understanding the principles of bone and joint healing can be realized when little evidence exists to guide a treatment decision. In the age of evidence-based medicine, surgeons may be obligated to base decisions on basic science rather than clinical evidence. The translation of basic science findings into clinical practice has been traditionally applied throughout the practice of fracture care, and can be appreciated in the works of Urist and McLean,109 Young,119 Perren,82 and McKibbin.66 These seminal findings still form the foundations for both clinical treatment and scientific understanding of bone and joint injuries.

Components of Fracture Healing

Fracture healing is a complex and dynamic process. One of the unique characteristics of bone repair is that the bone heals with new tissue that is indistinguishable from its preinjured state. Further, bone repair occurs in the vast majority of cases, with most fractures, treated in a myriad of ways, progressing to union. However, delayed union and nonunion
remain clinically significant issues, with nearly 10% of fractures having some degree of impaired healing. It has been reported, for example, that 4.5% of tibia fractures exhibit delayed healing and overall 2.5% of tibia fractures fail to unite. Fractures heal through the parallel processes of endochondral and intramembranous ossification, with most fractures exhibiting both types of healing. The fracture repair process is intimately influenced by the mechanical and biologic environments at the fracture site. While many of the factors that cause impaired healing are not within the control of the surgeon, it is increasingly appreciated that bone repair can be affected by surgical approaches. In order to best understand the healing response, surgeons should understand the basic components of cellular and molecular repair. These components can be categorized as cells and tissues, scaffold, blood supply, and molecules and their receptors (summarized in Table 4-1). Subsequent sections will further describe the coordination of these components in the process of fracture healing and how disruptions can negatively affect healing.

Cells and Tissues Involved in Fracture Healing

**Progenitor Cells (Periosteum and Endosteum)**

Bone surfaces are covered by tissue layers called the periosteum (outer layer) and the endosteum (inner layer), both of which are distinct fibrous layers rich in cells and blood vessels. It has been recognized for nearly a century that the periosteum responds to fracture through extensive cellular proliferation. The resulting pluripotent cells differentiate into either osteoblasts or chondrocytes, depending on inflammatory signals and the local mechanical and vascular environment, with increased mechanical stability favoring osteogenic differentiation. It has been shown that the periosteum provides a supply of osteoblasts, and is the primary source of chondrocytes, during fracture healing. In contrast, the endosteum is more restricted in its potential and appears to primarily give rise to osteoblasts during fracture healing. The results of an early case-control study suggested that the integrity of the vascularity and the periosteum related to initial fracture displacement played a role in improving fracture healing. Subsequent animal studies have investigated fracture healing following extraperiosteal or subperiosteal dissection, and found that the callus of extraperiosteally dissected osteotomy sites demonstrates decreased callus mineralization and inferior mechanical characteristics more similar to that of soft tissue. Further work has demonstrated that the violation and elevation of the periosteal sleeve about the fracture site is associated with a decreased bending moment and bending rigidity in a rat femur fracture model. In clinical practice, these studies have led to the belief that the disruption of the periosteum leads to failures of healing through the invasion of fibrous tissue and loss of fracture hematoma contents into the surrounding soft tissues. The emerging concept of biologic fracture fixation is aimed at reducing the potentially deleterious effects due to soft tissue stripping at the fracture site.

**Chondrocytes**

Chondrocytes, while usually associated with articular cartilage, also play an important role in the healing of fractures. The function of chondrocytes is to produce extracellular matrix (ECM) proteins such as proteoglycans and collagen, and during fracture healing, hypertrophic chondrocytes participate in endochondral ossification through the synthesis of matrix and the deposition of intracellular calcium. Early in the process, chondrocytes are identified by the expression of type II collagen and SOX-9, and the synthetic activity of chondrocytes is determined in vitro by quantifying proteoglycan and hydroxyproline production.

**Table 4-1 The Essential Components of Fracture Healing**

<table>
<thead>
<tr>
<th>Components</th>
<th>Importance in Fracture Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cells</td>
<td>Debride necrotic tissues</td>
</tr>
<tr>
<td></td>
<td>Signal for upregulation of synthetic functions</td>
</tr>
<tr>
<td></td>
<td>Form repair tissues</td>
</tr>
<tr>
<td></td>
<td>Remodel healed bone for optimal strength/weight ratio</td>
</tr>
<tr>
<td>Scaffold</td>
<td>Support cellular function</td>
</tr>
<tr>
<td></td>
<td>Inflammatory cell chemotaxis</td>
</tr>
<tr>
<td></td>
<td>Scaffold for mineralization</td>
</tr>
<tr>
<td>Blood Supply</td>
<td>Supply inflammatory cells to injury site</td>
</tr>
<tr>
<td></td>
<td>Deliver building blocks of repair tissues</td>
</tr>
<tr>
<td></td>
<td>Reverse hypoxic environment</td>
</tr>
<tr>
<td>Molecules</td>
<td>Regulate cellular function and proliferation during fracture healing process</td>
</tr>
</tbody>
</table>
Morphologically, chondrocytes in fracture callus are ovoid cells surrounded by ECM. During fracture healing chondrocytes hypertrophy as they terminally differentiate and develop intracellular calcium deposits before undergoing apoptosis. Chondrocytes subsequently undergo apoptosis, leaving a bed of woven bone that is invaded by new blood vessels and remodeled by osteoblasts and osteoclasts.

**Osteoblasts**

An osteoblast is defined by its ability to produce osteoid, the organic component of bone composed primarily of type I collagen. Osteoblasts line the surfaces of bone where they perform their functions of forming bone matrix and regulating the process of bone turnover by influencing osteoclast activity. Differentiating cells in the periosteum and endosteum provide a local source of osteoblasts at the fracture site.

On histologic examination, osteoblasts appear basophilic as a result of the abundant endoplasmic reticulum contained in the cytoplasm. This reflects the major role these cells play in protein production. Osteoblasts primarily produce type I collagen, osteocalcin, bone sialoprotein, and other matrix proteins associated with bone. In addition, osteoblasts express alkaline phosphatase, a membrane-bound enzyme responsible for dephosphorylation, an enzymatic activity that is often used as an assay for osteoblast activity in vitro.

**Osteoclasts**

Osteoclasts are the cell population responsible for the resorption of bone enabling the remodeling of fractures. Osteoclasts are derived from pluripotent hematopoietic stem cells of the macrophage/monocyte lineage. They are distinguished from other cells by the expression of tartrate-resistant acid phosphatase (TRAP) and cathepsin K. Other proteins associated with osteoclasts are calcitonin receptor and receptor activator of nuclear factor-kappa beta ligand (RANKL). 12

Histologically, osteoclasts are large, multinucleated cells that are formed by the fusion of mononuclear cells. Intracellular lysosomal vesicles and numerous mitochondria dot the cytoplasm of osteoclasts, and provide for the resorption of mineralized bone matrix. On bone surfaces, osteoclasts reside in Howship lacunae, or resorption pits in the bone surface.

**Inflammatory Cells**

Several inflammatory cell populations are associated with the cell-mediated and humoral responses to bone injury. Platelets, neutrophils, macrophages, and leukocytes are all found at the fracture site within the first hour after fracture. 96 Platelets are small cell fragments that are derived from megakaryocytes and are present in circulating blood and the spleen. Platelets are activated after fracture by encountering injured epithelial cells with exposed collagen and von Willebrand Factor (vWF). The activation of these factors results in the aggregation of platelets, blood coagulation, and the excretion of granule contents, which include platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF-1), and platelet-derived endothelial growth factor (PDGF). All of these trophic factors are putative mediators of the healing response and none of these factors alone has the synergistic effect of the myriad platelet-released growth factors. Therefore, platelets have a role in both hemostasis and the early local fracture healing process.

Polymorphonuclear leukocytes (PMNs) or neutrophils are the most abundant form of granulocytes in the peripheral blood. Histologically, they are distinguished by a multilobed nucleus and cytoplasmic granules. Under normal conditions PMNs circulate in the bloodstream making up 75% of the white blood cell mass. After tissue trauma, PMNs arrive immediately, and their numbers continue to increase at 4 hours after injury. 96 PMNs invade traumatized tissues in response to chemotactic signals and vessel endothelium cell surface capture mechanisms at the site of injury, including selectins and integrins. After activated PMNs have extravasated into the target tissue, their life span is only 1 to 2 days. Activated PMNs perform both phagocytic and degranulation functions at the site of trauma. Reducing the number of PMNs at the fracture site leads to reduced callus rigidity in a rat femur osteotomy model, suggesting neutrophil actions negatively impact endochondral ossification. 39 It may be that this effect is caused by an increase in reactive oxygen species at the fracture site. Alternatively, PMNs could be providing an inhibitory cytokine signal to bone forming cells as fracture healing progresses, although the cytokines produced by PMNs, including C-C motif chemokine 2 and interleukin (IL)-6, are generally thought to enhance fracture repair. 113,117

Macrophages and precursor monocytes closely follow PMNs, arriving at the fracture site after several hours. Resident tissue macrophages may even participate at the earliest stages of fracture healing given their location nearer the site of the fracture. 83 Macrophages and monocytes are derived from the hematopoietic stem cell lineage and are traditionally thought to play a role in the debridement of tissue injury sites. Macrophages also play a role in the activation of the adaptive immune system through the presentation of antigens on the cell surface and the secretion of cytokines. Resident tissue macrophages may also play a role in the regulation of bone formation and local tissue homeostasis. 4

Lymphocytes, including various subpopulations of B-cells and T-cells, form the adaptive immune system. As granulation tissue develops at the fracture site about 7 days after fracture, the number of T-cells eclipses that of macrophages. The main contribution of lymphocytes to fracture healing appears to be the production of cytokines. This contribution appears to be inhibitory, as the ablation of the adaptive immune system leads to improved endochondral bone healing in a rat model. 102

**Mesenchymal Stem Cells**

An area of intense clinical interest is the therapeutic potential of mesenchymal stem cells (MSCs) in fracture healing
applications, such as nonunion and critical sized defects. MSCs were first identified as a population of marrow-derived, adherent cells capable of colony formation in vitro. Subsequently, the definition of MSCs has tightened to include the requirement of differentiation of the cells into bone, cartilage, and adipose tissue in vitro. Osteoblastic differentiation in cell culture is stimulated by the inclusion of dexamethasone, β-glycerol phosphate, and ascorbate-2-phosphate in the cell culture medium. Chondrogenic differentiation is encouraged by culturing cells in a pellet in the presence of dexamethasone, insulin-transferrin-sodium selenite (ITS), ascorbate-2-phosphate, sodium pyruvate, proline, and TGF-β. Adipogenic differentiation requires a medium containing dexamethasone, isobutylmethylxanthine (IBMX), and insulin. MSCs reside in defined tissue reservoirs, or niches, within the body, including bone marrow, adipose tissue, and the synovial lining. In addition, vascular pericytes and muscle cells exhibit the ability to express osteogenic markers given the appropriate stimulus and, although they may not be considered MSCs, they may also contribute to bone healing. MSCs are identified histologically as fibroblast-like cells that grow to confluence in culture and express specific cell surface antigens. MSCs participate in the healing of fractures by supplying a cell population capable of differentiating into chondrocytes or osteoblasts based on local cytokine queues and mechanical environments. MSCs are also present at the fracture site as they reside in adjacent bone marrow niches. Therefore, MSCs are not necessarily recruited to the fracture site, but rather resident MSCs may proliferate and differentiate in response to the evolving cytokine milieu of the fracture hematoma.

Despite claims of the therapeutic benefit of injected MSCs in the stimulation of fracture repair, experimental evidence suggests that circulating MSCs play a minor role, if any, in fracture healing. Circulating cells expressing markers of osteogenic potential have been identified. However, the injection of ex vivo cultured MSCs expressing a green fluorescent protein (GFP) marker into a rabbit fracture model did not yield an accumulation of labeled cells at the fracture site. In a more definitive study, a mouse constitutively expressing GFP and a fluorescent protein into a rabbit fracture model did not yield an accumulation of labeled cells at the fracture site. The central role of muscle to fracture healing is well established. When bone is fractured, local blood vessels are disrupted, creating a relatively avascular and hypoxic area within the fracture hematoma and the early fracture callus. The hypoxic environment hypoxia-inducible factor (HIF)-1 promotes the production of vascular endothelial growth factor (VEGF), promoting revascularization. The absence of competent blood vessels crossing the fracture site necessitates angiogenesis during the process of bone repair. For vascular repair to proceed concurrently with bone healing, the newly forming matrix must be degraded in concert with the proliferation of endothelial cells. Mechanistically, it may be that the failure of MMP9 knockout mice to replace cartilage with bone is related to the failure of vascular invasion.

**Scaffold**

Bone healing is a three-dimensional process that requires a scaffold to allow the cellular components of the healing process to perform their functions. This scaffold, or ECM, is responsible for conferring the structural properties of bone and cartilage as well as serving in some cell regulatory functions. The ECM of bone is composed primarily (60% to 70%) of inorganic material in the form of mineral crystals containing calcium, phosphate and other ions including sodium, magnesium, and carbonate. The organic portion of bone (30% to 40%) consists primarily of type I collagen (90%) with the remainder being made up of other types of collagen and several noncollagenous proteins. Important noncollagenous proteins involved directly in bone healing include osteocalcin, bone sialoprotein, proteoglycans, and matricellular proteins. When the organic phase of bone is not mineralized it is termed osteoid.

Immediately after fracture, the conversion of fibrinogen to fibrin creates a semisolid blood clot in the fracture site that provides the initial scaffold for inflammatory cell migration. During the rest of fracture repair, the ECM must be constantly remodeled to allow for the restoration of functional anatomy. An extreme example, endochondral ossification is a process where a cartilage scaffold rich in type II collagen is completely replaced by bone. In order to allow the rapid reorganization of tissue types in the ECM, matrix metalloproteinases (MMPs) such as collagenases, gelatinases, stromelysins, and other catabolic enzymes like cathepsins, are required to work in parallel with synthetic processes. In fact, there is evidence that the absence of MMPs, particularly MMP9, results in nonunion associated with the failure to replace cartilage with osteoid at the fracture site.

**Blood Supply**

The central role of the vasculature in fracture healing is well established. When bone is fractured, local blood vessels are disrupted, creating a relatively avascular and hypoxic area within the fracture hematoma and the early fracture callus. In the hypoxic environment hypoxia-inducible factor (HIF)-1 promotes the production of vascular endothelial growth factor (VEGF), promoting revascularization. The absence of competent blood vessels crossing the fracture site necessitates angiogenesis during the process of bone repair. For vascular repair to proceed concurrently with bone healing, the newly forming matrix must be degraded in concert with the proliferation of endothelial cells. Mechanistically, it may be that the failure of MMP9 knockout mice to replace cartilage with bone is related to the failure of vascular invasion.
Table 4-2 Molecules Important in the Fracture Healing Process

<table>
<thead>
<tr>
<th>Molecules</th>
<th>Source Cells</th>
<th>Effector Cells</th>
<th>Effect on Fracture Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Morphogenetic Protein-2</td>
<td>Persistent cambial layer, macrophages, osteoprogenitors, bone, and cartilage matrix</td>
<td>Osteoblast and osteocytes in new woven bone</td>
<td>Stimulates differentiation of chondroprogenitor and osteoprogenitor cells in early fracture healing</td>
</tr>
<tr>
<td>BMP-2</td>
<td></td>
<td>Osteoclast Precursors</td>
<td>induces resorption of calcified cartilage and stimulates osteoclast activity</td>
</tr>
<tr>
<td>Receptor Activator of Nuclear Factor-Kappa Beta Ligand</td>
<td>Osteoblast, lymphocytes</td>
<td>Osteoprogenitor cells</td>
<td>Stimulates osteoblast proliferation and differentiation</td>
</tr>
<tr>
<td>RANKL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin-like Growth Factor-1</td>
<td>Osteoprogenitor, bone matrix</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet-derived Growth Factor</td>
<td>Degranulating platelets, fracture hematoma macrophages</td>
<td>Chondroprogenitor and osteoprogenitor cells</td>
<td>Stimulates migration of progenitor cells and osteoblast</td>
</tr>
<tr>
<td>PDGF</td>
<td>Platelets, bone, and cartilage matrix</td>
<td>Chondroprogenitor and osteoprogenitor cells</td>
<td>Stimulates progenitor cell proliferation</td>
</tr>
<tr>
<td>Transforming Growth Factor Beta</td>
<td>Macrophages, chondrocytes, and osteoblast</td>
<td>Chondroprogenitor and osteoprogenitor cells</td>
<td>Stimulates progenitor cell proliferation</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Parathyroid gland (chief cells)</td>
<td>Chondrocytes</td>
<td>Recruits and activates chondrocytes in the early fracture callus</td>
</tr>
<tr>
<td>Fibroblast Growth Factor (FGF)</td>
<td></td>
<td></td>
<td>Angiogenesis, chemotactic for macrophages and endothelial cells and vasodilation</td>
</tr>
<tr>
<td>Vascular Endothelial Growth Factor</td>
<td>Platelets, hypertrophic chondrocytes</td>
<td>Macrophages, endothelial cells and granulocytes</td>
<td></td>
</tr>
<tr>
<td>VEGF</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Molecules**

Given the complexity of the healing response to a fracture, an intricate communication system is required to regulate the actions of participating cells. Cellular interactions are primarily mediated through the actions of molecules termed cytokines through receptors on effector cell surfaces. Although detailing all of the cytokine–receptor interactions at play during the healing of a fracture is beyond the scope of this chapter, there are several molecules that require a detailed explanation of the mechanism of action given their use in clinical applications or their future potential as targets to improve fracture healing and treat nonunion (Table 4-2).

Perhaps the molecules with the most controversial and clinically relevant role in fracture healing are the bone morphogenetic proteins (BMPs). The concept of osteoinduction and the role of BMPs in this process were discovered by Urist in 1965 when he observed that intramuscularly implanted demineralized bone induced the ectopic formation of bone. The number of unique isoforms of BMP, all members of the TGF-β superfamily, has now surpassed 16. The BMPs act on cells during fracture healing through heterodimers of type I and type II transmembrane receptors, which are serine/threonine kinases. After the binding of BMPs, activated BMP receptors phosphorylate cytoplasmic proteins of the Smad family, which in turn regulate the expression of downstream target genes that affect cellular processes such as proliferation and differentiation.

BMPs are antagonized by noggin, a protein that binds BMP-2, BMP-4, and BMP-7, rendering them inactive. Noggin expression is increased in osteoblasts in response to BMP-2 receptor activation by BMP-2 suggesting that noggin and BMP-2 form a negative feedback loop. In addition, in rodent models of nonunion the expression of chordin, another BMP antagonist, is upregulated, suggesting that the balance between BMPs and BMP antagonists must be tightly regulated during fracture healing, possibly representing a therapeutic target for the enhancement of fracture healing.

Activation of receptor activator of nuclear factor-kappa beta (RANK) by RANKL is the final signaling step in the production of osteoclasts from progenitor cells. Given the important role of osteoclasts in the remodeling of bone, this receptor–ligand pair has been a target for the treatment of osteoporosis. Experimental evidence suggests that antagonizing RANK signaling does not interfere with the early fracture healing process nor does it prevent the formation of bridging callus. In that study, however, there was a marked delay in the mineralization of cartilage in unstable fractures. The authors proposed that the delay in mineralization was due to the reduced number of blood vessels in the callus. Others have found similar results and confirmed that inhibition of osteoclast differentiation by RANKL antagonism or inhibition of function through bisphosphonate treatment after fracture results in improved mechanical properties of the fracture callus despite delayed mineralization.

With increasing interest in the clinical applications of platelet-rich plasma in musculoskeletal repair, the effects of PDGF on fracture repair have received some attention. PDGF is found in the fracture site of humans early in the fracture repair process. On a cellular level, PDGF has been found to be associated with platelets, macrophages, fibroblasts, endothelial cells, and the bone matrix, suggesting a broad range of activities. The effects of PDGF on the bone healing process have also been investigated both in vitro and in vivo. These studies have shown that PDGF activates macrophages and stimulates angiogenesis, attracts fibroblasts and enhances collagen synthesis, and stimulates the proliferation of bone cells.
The exogenous supplementation of PDGF at the fracture site has also been examined in a rabbit osteotomy model with the findings of increased mineralization and increased bending strength when compared to controls. Another study in rats comparing the healing of tibia fractures after stabilization with control or PDGF-coated intramedullary wires showed accelerated radiographic union of fractures with PDGF, but the cellular rationale for these differences was not clear. Therefore, PDGF remains an experimental therapy with future promise for clinical use.

The role of growth hormone (GH) and IGF-1 in fracture healing has been investigated given the clinical availability of GH for the treatment of short stature. GH is released by the pituitary gland through the action of GH-releasing hormone. The main action of GH is to cause the systemic release of IGF, which has myriad biologic activities, including the stimulation of osteoblasts. Of particular interest is the paracrine activity of IGF-1 as a chemotactic factor for osteoblast migration. Employing a cell line of primary murine osteoblasts in culture, investigators demonstrated that an IGF-1 gradient enhanced the migration of osteoblasts. Given that osteoblasts also produce IGF-1, this molecule may be an important regulator of cell trafficking at the fracture site. Animal work investigating the potential therapeutic roles of both local and systemic GH and IGF-1 has shown mixed results with some studies demonstrating enhancement of fracture healing and others suggesting no effect of exogenously applied GH and IGF-1.

TGF-β has been shown previously to be expressed constantly during fracture healing. TGF-β is a member of a protein superfamily that encompasses the BMPs, growth and differentiation factors (GDFs), activins, and inhibins. TGF-β1 expression has been associated primarily with endochondral ossification, and it has a particularly high expression in the periosteum after fracture. In human fractures, it has been shown that serum TGF-β1 levels are significantly lower in patients with impaired healing than in those with normal healing, suggesting TGF-β1 may be a biomarker for an increased risk of nonunion. Clinically, however, the broad effects of TGF-β limit the use of TGF-β1 for fracture healing enhancement due to fears of unforeseen side effects upon other tissues and cell populations.

FGFs are members of another family of signaling molecules that are expressed throughout the body. Acidic FGF (FGF-1) and basic FGF (FGF-2) are the proteins most relevant to the fracture healing process. Both proteins are known for their angiogenic and cell activating properties and there has been interest in their potential clinical application for the enhancement of fracture healing. The actions of FGFs are transduced through transmembrane receptors. Mutations in these receptors have been identified as the genetic cause of several common skeletal dysplasias including achondroplasia, which involves a mutation in the FGF receptor-3 (FGFR-3) and severely affects endochondral ossification during skeletal development. During fracture healing, the local injection of recombinant human FGF-2 (rhFGF-2) accelerated early chondrocyte maturation and increased the proportion of intramembranous ossification in a study in beagles. The time to remodeling was also decreased in rhFGF-2 treated animals, suggesting that treatment accelerated the entire process of fracture healing, including remodeling. One well-designed randomized controlled trial has been conducted using rhFGF-2 as an adjunct to closed tibial fracture treatment. Although the authors did not show a difference in the rate of secondary procedures in this study, they did note an accelerated rate of union in fractures treated with a percutaneous injection of rhFGF-2. In addition, no adverse events were noted among the treated patients, suggesting the safety of the treatment, although further testing is necessary before there is widespread clinical acceptance of rhFGF-2 as an adjunct to fracture treatment.

**Types of Bone Healing**

**Endochondral**

During development, the process whereby a cartilaginous anlage is replaced by bone is referred to as endochondral ossification. This process typically occurs as the resident chondrocytes mature and senesce, and vessels invade the cartilage. In many ways fracture healing replicates this process of skeletal development. In unstable fractures, cartilage is found during the early phase of fracture healing and, as stated previously, chondrocytes hypertrophy and are replaced by osteoblasts as vessels invade the cartilage callus (Fig. 4-1). In the past, the predominance of endochondral ossification was referred to as secondary bone healing, which proceeded through three sequential phases: soft callus, hard callus, and remodeling. This healing response was associated with motion at the fracture site, such as can occur with cast treatment or incomplete stability.

![FIGURE 4-1 Ossification of the cartilage scaffold in endochondral ossification. In this Hall-Bryant quadruple stained section of a mouse tibia 10 days after fracture, the transition of cartilage callus to ossified tissue is demonstrated. In the upper right of the photomicrograph, typical chondrocytes can be seen. In the lower left, the red matrix denotes calcified tissue surrounding osteoblasts. Chondrocyte-like cells with calcium deposits in the cytoplasm can be visualized at the transition between the nonossified and the ossified cartilage scaffold.](image-url)
Intramembranous

The process of direct bone formation without a cartilaginous intermediate is referred to as intramembranous ossification. During skeletal development, intramembranous bone formation involves the direct deposition of osteoid by cells of mesenchymal origin. During fracture repair, intramembranous, or primary healing, results when the motion between two fracture surfaces is abolished through rigid internal fixation. Healing then progresses without the formation of visible fracture callus. Instead, fragments are united by the passage of osteoclast-led cutting cones across the fracture site along the long axis of the bone. The leading edge of the cutting cone is followed by osteoblasts that restore the lamellar architecture of cortical bone as evidenced by scant type I collagen at the fracture site.

Clinically, primary bone healing manifests as loss of the obvious fracture line with an absence of visible fracture callus on postoperative radiographs. These two forms of bone healing represent distinct processes. Modern fracture fixation techniques benefit from both types of healing in different circumstances. Neither form of bone repair can be regarded as inferior, with most fractures healing through a combination of the two types of healing. In addition, the time eventually required to restore the mechanical integrity of bones is not reduced by healing either through endochondral or intramembranous ossification. The influence of mechanical factors on the biology of fracture healing will be further elaborated below.

Stages of Enchondral Fracture Repair

A fracture results in a cascade of events aimed at restoring mechanical integrity to that unstable limb segment. The conventional way to define this process is through discrete stages of enchondral fracture healing including, inflammation, soft callus, hard callus, and remodeling (Figs. 4-2 to 4-4). These four stages, preceded by the early hematoma stage, will be presented in sequence here, although it is key to remember that they can overlap one another in time during the healing process, and different parts of any given fracture callus may exhibit different stages simultaneously, depending on the microenvironment to which individual cells are exposed (Fig. 4-5).

Hematoma Formation

The first consequence of fracture is a local structural disruption of the bone and the associated marrow, periosteum, surrounding muscle, and blood vessels (Fig. 4-2). These events lead to the accumulation of a fracture hematoma composed of the debris from these structures as well as platelets, erythrocytes, and immune cells extravasated from sheared blood vessels. Due to the lack of a vascular supply and increased cellular activity, the oxygen tension of a fracture hematoma is decreased significantly over the first 72 hours after fracture.

The fracture hematoma is bioactive. The transplantation of a 4-day old fracture hematoma to a remote subperiosteal or intramuscular location in rats results in ectopic formation of bone and cartilage, whereas putting a peripheral blood clot there does not result in a similar response. In addition, the removal of a fracture hematoma from a femoral fracture in a rat after 2 or 4 days resulted in mechanically inferior healing, and removal of the hematoma after 30 minutes has a similar result.

Others have demonstrated the immunologic activity of the fracture hematoma. As compared to the peripheral blood of fracture patients, the fracture hematoma contains seven-fold greater amount of membrane-bound tumor necrosis factor-alpha (TNF-α). The concentration of IL-6 and IL-8 in the fracture hematoma is also greatly elevated, whereas inflammatory cytokines are barely detectable in the plasma of these patients.
at 24 and 48 hours. These results support a role for the local inflammatory response in fracture repair, in contrast to the systemic response seen in polytraumatized patients. It is not clear what role the systemic inflammation plays upon the local environment during fracture repair.

**Inflammation**

The inflammatory stage of fracture repair dominates the cellular response during early healing. Although this response to injury often continues for a prolonged period, it is the initial pro-inflammatory environment that influences the progression

**FIGURE 4-3** Early repair of a diaphyseal fracture of a long bone. **A:** Drawing showing organization of the hematoma, early woven bone formation in the subperiosteal regions, and cartilage formation in other areas. Periosteal cells contribute to healing this type of injury. If the fracture is rigidly immobilized or if it occurs primarily through cancellous bone and the cancellous surfaces lie in close apposition, there will be little evidence of fracture callus. **B:** Photomicrograph of a fractured rat femur 9 days after injury showing cartilage and bone formation in the subperiosteal regions. (Reprinted from: Einhorn TA. The cell and molecular biology of fracture healing. Clin Orthop Relat Res. 1998;335(suppl):S7–S21, with permission.)

**FIGURE 4-4** Progressive fracture healing by fracture callus. **A:** Drawing showing woven or fiber bone bridging the fracture gap and uniting the fracture fragments. Cartilage remains in the regions most distant from ingrowing capillary buds. In many instances, the capillaries are surrounded by new bone. Vessels revascularize the cortical bone at the fracture site. **B:** Photomicrograph of a fractured rat femur 21 days after injury showing fracture callus uniting the fracture fragments. (Reprinted from: Einhorn TA. The cell and molecular biology of fracture healing. Clin Orthop Relat Res. 1998;335(suppl):S7–S21, with permission.)
of healing. As a result of the initial energy imparted during a fracture, there is extensive damage to bone and the surrounding tissues, shearing of local blood vessels, and a variable disruption of the integrity of the periosteum. As a result, the area immediately adjacent to the fracture site becomes relatively hypoxic and localized tissue necrosis occurs.\(^2\)

The presence of cellular debris initiates an inflammatory response mediated by both local and infiltrating inflammatory cells, including platelets, polymorphonuclear cells (PMN), macrophages, and lymphocytes. These cells help orchestrate the subsequent healing process by phagocytosing necrotic tissue and by producing cytokines that influence the repair process. Neutrophils are the first cells to arrive at the fracture site, and are present at least as early as 3 hours after fracture.\(^13\)

Even at this early phase of fracture healing, markers of osteogenic differentiation can be detected at the site, reinforcing the concept that the various stages of fracture repair occur in continuum rather than as distinct steps.\(^2\) Clinicians should note that surgical interventions typically occur during this early phase of fracture healing, and therefore they can disrupt the hematoma or inflammatory stages of fracture healing. Animal models have demonstrated that the removal of hematoma early during fracture repair (2 to 4 days) and repeated debridement of the fracture site (for the first 2 days) after fracture can result in both delayed union and nonunion.\(^40,32,80\)

### Soft Callus

The soft callus stage of fracture healing is heralded by the differentiation of progenitor cells into chondrocytes and osteoblasts (Fig. 4-3). This stage begins at the end of the first week after fracture in a murine model, and typically by 3 weeks in humans. Depending on the mechanical environment and the vascular supply to the fracture site, cartilage or osteoid becomes the predominant tissue in the callus, replacing the fibrous tissue and hematoma. Types I and II collagen are produced in order to form a matrix that restores stability to the bone ends. Mechanical testing of the fracture callus at this stage reveals the stability of soft tissue rather than a consolidated mass that confers bone stability. Radiographically, the fracture site does not appear united at this stage, but a fluffy appearance of the early mineralizing callus may start to be detected.

#### Hard Callus

The hard callus stage is defined by the conversion of cartilage to a calcified cartilage matrix with terminal differentiation of the chondrocytes (Fig. 4-4). This occurs during the second week in murine tibia fracture models and several weeks after a fracture in humans. Concurrently, with the wave of calcification, hypertrophic chondrocytes senesce and blood vessels invade the callus. Given the reduction in the number of chondrocytes, the dominant cell types during the hard callus phase are the osteoblast and osteoclast. The woven bone deposited at this time by the osteoblasts further strengthens the callus, but does not follow the stress-induced pattern seen in the surrounding, intact bone. The reduction in strain that occurs at this point in the bridging bone appears to have a molecular effect on both bone cells and newly forming vessels. Clinically, this phase of healing is seen as the calcification and consolidation of the fracture callus on radiographs. During cast or traction treatment of fractures, the hard callus phase is also accompanied by a clinically evident reduction in pain and increased sense of stability at the fracture site.

#### Remodeling

The remodeling phase is the phase of bone healing that returns the previously damaged tissue nearer to its pre-injured state. During remodeling, the canalicularchitecture of bone is re-established, and the haversian system with its osteocytes is restored. This process starts in concert with bone consolidation and continues for months or years after a solid osseous union has been achieved. During remodeling, intricate communication between osteoblasts and osteoclasts leads to the creation of lamellar bone consistent with the mechanical stress imposed on the bone by loading, particularly weight bearing. This phenomenon, described by Wolff’s law, involves the strengthening of the internal and cortical architecture of bones in response to applied
loads. In order to accomplish the stress-induced remodeling of bone, the actions of osteoclasts and osteoblasts are coupled in the functional unit of bone remodeling—the cutting cone (Fig. 4-6). Cutting cones are formed by osteoclasts that first remove the disorganized woven bone. Then osteoblasts follow and lay down lamellar bone in an organized pattern around a central blood vessel. The activity of bone resorption by osteoclasts and bone formation by osteoblasts is linked through the actions of RANK, RANKL, and osteoprotegerin (OPG). As RANKL exists primarily as a membrane-bound protein, binding to RANK is usually limited. The soluble RANKL concentration is increased by the presence of IL-1β, IL-6, TNF-α, vitamin D3, parathyroid hormone (PTH), and other cytokines, and the subsequent cleavage of membrane-bound RANKL by proteolytic processing or altered gene expression. Binding of RANKL to RANK results in the differentiation and activation of osteoclasts. The role of OPG in this pathway is as a receptor decoy for RANKL. OPG competes for the binding of RANKL, thereby effectively reducing activity in osteoclasts and osteoclast progenitors and decreasing bone resorption. Through this molecular connection, the balance of bone resorption and formation can be coordinated to restore the structural integrity of the damaged tissue.

**Mechanical Influences on Bone Healing**

Early clinical observations led to the belief that fracture stability influenced healing. Subsequent experimental evidence demonstrates that the mechanical environment plays a role in determining the cellular events that define bone repair. Mechanical instability at the fracture site favors endochondral ossification (i.e., the formation of cartilage prior to ossification), whereas mechanical stability results in fracture healing through intramembranous ossification (i.e., direct or primary bone formation) (Fig. 4-7). Classical teaching refers to the concepts of primary (direct) and secondary (indirect) bone healing. Both primary and secondary bone healing have specific roles in the repair of specific fracture patterns and treatments. Given the wide range of implant options now available for the treatment of fractures, it is important to understand the biologic implications of various forms of fixation.

In one study, a 10-day delay in the stabilization of fractures in rabbits was shown to enhance fracture healing. However, a 4-day delay did not enhance fracture repair or callus mechanics in another study in mice. The histologic examination of the fracture calluses demonstrated an increased predominance of cartilage 14 days after fracture when the fracture stabilization was delayed 24 hours or greater, suggesting that cell fate is determined early in the fracture healing process. When considering the closed management of fractures, one can appreciate that the cellular elements in the fracture hematoma have already acted on local progenitor cells at the time of treatment, and therefore, some degree of endochondral ossification should be expected and a callus should be seen on radiographs. After the open reduction and rigid internal fixation of fractures, the initial fracture hematoma typically has been removed, and
therefore a new population of progenitor cells responds to the altered fracture environment through intramembranous ossification, with the subsequent absence of visible callus on postoperative radiographs.

**Failures of Healing—Etiologies and Overview of Treatment Strategies**

Failures of healing fall into two broad categories with associated cellular mechanisms: Biologic and mechanical failures. The two different nonunion etiologies are recognized clinically by the appearance of atrophic or hypertrophic nonunions, respectively. The natural history of failure of healing is nonunion, an ill-defined term meant to signify the failure of a fracture to achieve stability through bridging bone. Atrophic nonunion is defined by the absence of any visible bone formation on radiographs. Hypertrophic nonunion is defined by abundant bone formation without bone bridging the fracture site. Oligotrophic nonunion is defined as failure to bridge the fracture site with only a moderate amount of bone formation adjacent to a visible fracture line. Delayed union represents the situation where healing is prolonged compared to that expected for a given anatomic location.

**Atrophic Nonunion**

The major factors that contribute to atrophic nonunions include, infection, compromised nutrition, smoking, medications, and surgeon-controlled factors such as fracture vascularity. These modifiable risk factors for impaired fracture healing will be reviewed below.

Nutritional status remains an important component in the workup of patients presenting with an atrophic nonunion. Fracture healing is an anabolic process requiring molecular building blocks and substantial energy. Leung et al. showed that the fracture callus in rabbits 2 weeks after fracture contains 1,000-fold more adenosine triphosphate than that of normal bone. Malnutrition can also lead to deficiencies in cofactors necessary to catalyze important reactions during fracture healing. Research has shown that up to 18% of hip fracture patients are clinically malnourished, and these malnourished patients stay in the hospital longer and are less likely to recover to pre-injury functional levels.

Poor nutrition is indicated by low serum albumin levels, low iron binding capacity, and decreased systemic lymphocyte counts. Failure to correct nutritional deficiencies can expose traumatized patients to an increased risk of impaired wound and fracture healing, and other complications.

The use of tobacco has been implicated in delays in open tibia fracture healing, and in the consolidation of osteotomies performed for hallux valgus deformity correction. Tobacco in cigarettes contains over 4,000 chemicals, and the most prominent of these compounds is the cholinergic stimulant, nicotine. In animal studies, the administration of pure nicotine orally or subcutaneously has been shown to increase fracture callus strength and subcutaneous administration also showed an increase in bending stiffness in a rat femur fracture model. Orally administered tobacco extract without nicotine, however, reduced strength, ultimate torque, and torque at yield point. A recent review has postulated that the key to the delay in fracture healing seen in smokers may be through the cholinergic anti-inflammatory pathway and associated
inhibition of TNF-α in smokers. This divergence of opinion suggests that further clarification is needed to determine the effects of the individual components of tobacco products on fracture healing, and smokers should be counseled to abstain from smoking during the fracture healing process. However, it is still unclear if transdermal nicotine patches are contraindicated as an adjunct to cessation strategies in fracture patients who smoke.

The chronic use of corticosteroids is known to have detrimental effects on bone mineral density after prolonged administration. The cellular effects of corticosteroids include the inhibition of osteogenic differentiation of MSCs, osteoblast and osteocyte apoptosis, and a reduction in organic matrix synthesis. Taken together, these effects of corticosteroids should interfere with processes central to fracture healing and increase individual susceptibility to fracture. However, mixed results have been found in animal studies on the effects of corticosteroids upon fracture healing. At a minimum, alterations in bone quality after prolonged use do increase the difficulty in operatively treating corticosteroid-associated fractures, and the systemic effects of this class of therapeutic agents expose patients to higher rates of complications as a result of immunosuppression.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications. Given the pain and inflammation associated with musculoskeletal injuries, NSAIDs can be a useful addition to the analgesic armamentarium of physicians treating fractures. While the perioperative use of NSAIDs has been associated with impaired healing in spinal fusion patients, a recent meta-analysis of available clinical trials failed to convincingly support the hypothesis that NSAID use increases the risk of nonunion. NSAIDs reduce inflammation through the inhibition of cyclooxygenases (COX). The COX-2 isoform of the enzyme has been shown to stimulate bone formation through the action of prostaglandin E2 (PGE2) and the subsequent upregulation of Cbfal (or Runx2), a transcription factor necessary for osteoblastogenesis. Despite the link between the genetic loss of COX-2 activity and impaired fracture healing, studies where animals with fractures are administered NSAIDs have not definitively demonstrated impaired healing with both non-specific and COX-2–specific NSAIDs. Therefore, current guidelines suggest that the clinician weigh the current theoretical risk of impaired fracture healing against the benefits of improved pain relief.

**Hypertrophic Nonunion**

The development of a hypertrophic nonunion is generally related to a lack of adequate stability at the fracture site. As stated above, motion at the fracture site favors the differentiation of progenitor cells into chondrocytes. In addition, macroscopic movement of fracture fragments prevents normal vascular invasion and the associated senescence of chondrocytes and mineralization of the cartilage matrix seen in optimally stable fractures. Morphologically, hypertrophic nonunions are identified by a persistent fracture line with a large fusiform callus that has been compared to the shape of two elephants’ feet, sole-to-sole. With revision surgery to provide adequate stability, a hypertrophic nonunion typically goes on to heal uneventfully without the need to augment local biology with bone graft or growth factor stimulation.

**Systemic Pharmacologic Treatments Influencing Bone Healing**

Bisphosphonates are a class of drug commonly used to decrease the risk of fracture in patients with low bone mineral density. The molecular structure of bisphosphonates is similar to that of pyrophosphate, an essential component of the mineral phase of bone. Bisphosphonates are incorporated into the lattice structure of bone and inhibit osteoclast function, thereby limiting bone turnover in the steady state. After bone fracture, bisphosphonates do not appear to interfere with the early phases of repair, rather continued bisphosphonate use in one study resulted in a larger, stronger callus. Although time-to-union was not affected, a marked delay in the completion of remodeling was seen, and the authors of this study proposed that the enlarged callus was an adaptation to this delay.

Parathyroid hormone (PTH), an endogenously occurring regulator of calcium, phosphate, and vitamin D homeostasis, has been shown in animal studies to enhance fracture healing when given intermittently. Teriparatide, the 1 to 34 amino terminus of the 84 amino acid endogenous protein, has also been shown to possess biologic activity similar to the native protein and is FDA-approved for the treatment of osteoporosis. In a rat femur fracture model teriparatide was found to increase the external callus volume and the ultimate load to failure of the femoral fracture callus while concurrently increasing bone mineral density in the opposite femur. Although not completely elucidated, the mechanism of improved fracture healing with PTH treatment is felt to relate to the increase in chondroprogenitor and osteoprogenitor cells in the early fracture callus. Further research has shown that the stimulatory effects on chondroprogenitor cell proliferation are noted early in the fracture healing process, with both proliferation rates and the expression of chondrocyte maturation-related genes (SOX-9, pro-1α [II] collagen, pro-1α [X] collagen, and osteopontin) normalizing by the soft callus phase of healing. At a molecular level, the canonical Wnt pathway appears to drive the beneficial effects of teriparatide on fracture healing by accelerating the maturation of chondrocytes through the nuclear localization of β-catenins.

**Cartilaginous Healing**

**Cartilage Healing Response to Isolated Chondral Injury**

The body does not heal isolated cartilage damage effectively. This defective healing response is attributable to the lack of a blood supply necessary for the initiation and support of the repair process, a lack of sufficient stem cells to repopulate...
and repair the defect, and chondrocyte cell death in the surrounding cartilage which compromises tissue integrity and interferes with repair tissue integration. Viable chondrocytes near the injury may proliferate, form clusters of new cells, and synthesize new matrix, but chondrocytes cannot migrate readily through cartilage tissue to the site of the injury, and the matrix components they synthesize usually are not sufficient to fill the defect.

Cartilage Healing Response to Osteochondral Injury

Articular injuries that also disrupt the subchondral bone initiate the fracture healing process within the subchondral bone, and the repair tissue from the bone can fill the overlying cartilage defect. Cartilage healing then follows the sequence of inflammation, repair, and remodeling like that seen in bone or dense fibrous tissue. Blood from ruptured subchondral vessels fills the injury site with a hematoma that extends from the area of bony injury into the chondral defect. Inflammatory cells migrate through the clot followed by fibroblasts that begin to synthesize a collagenous matrix. Within the repair tissue, some of the cells assume a rounded shape and begin to synthesize a matrix that has some properties of articular cartilage.

Within a few weeks of injury, the repair tissue forming within the defect begins to undergo differentiation into cartilaginous and osseous tissues. This cartilage tissue is a mixture of fibrocartilage and variable amounts of hyaline-like cartilage. While the initial repair of an osteochondral injury typically follows a predictable course, subsequent changes in the cartilage repair tissue vary considerably among similar defects. In some chondral defects the production of a cartilaginous matrix continues, and the cells may retain the appearance and some of the functions of articular chondrocytes, including the production of some type II collagen and proteoglycans. However, the composition, structure, and organization of normal articular cartilage is never recreated. Instead, the end product is a fibrocartilaginous scar that may still provide clinically satisfactory joint function for many years. Unfortunately, in many injuries, the cartilage repair tissue deteriorates more rapidly. The cells lose the appearance of chondrocytes and appear to become more fibroblastic, and the fibrous matrix fibrillates and fragments (Fig. 4-8).

Factors Influencing Cartilage Healing

Gap: A primary objective of surgery is to close the diastasis between fracture fragments, and it is reasonable to expect that

---

**FIGURE 4-8**

A: Normal rabbit articular cartilage showing the homogeneous extracellular matrix. The chondrocytes near the articular surface are relatively small and flattened, in which those in the middle and deeper zones of the articular cartilage have a more spherical shape. B: Well-formed fibrocartilaginous repair cartilage. Notice that the extracellular matrix is more fibrillar and the chondrocytes do not show the same organization as normal articular cartilage. Nonetheless, this repair cartilage does fill the defect in the articular surface. In most instances after osteochondral injury, this type of tissue forms within 6 to 8 weeks. C: Photomicrograph showing fibrillation and fragmentation of fibrocartilaginous repair tissue. Because fibrocartilaginous repair tissue lacks the mechanical properties of normal articular cartilage, it often degenerates over time. (Reprinted from: Buckwalter JA, Mow VC. Cartilage repair and osteoarthritis. In: Moskowitz RW, Howell DS, Goldberg VM, Mankin HJ, eds. Osteoarthritis Diagnosis and Medical/Surgical Management. 2nd ed. Philadelphia, PA: WB Saunders, 1992:86–87, with permission.)
minimizing the volume and surface area of a chondral defect would increase the probability of successful cartilage repair. Experimental work indicates that 1-mm or smaller defects tend to heal more successfully than larger defects. However, some residual separation of osteochondral fragments or the loss of segments of the articular surface may not always produce clinically significant disturbances of joint function or rapid cartilage deterioration. The extent of tolerable loss of the articular surface has not been defined and may vary among joints.

Step-off: Residual step-off of the articular surface can cause instability, locking, catching, and restricted range of motion. Some degree of step-off can be corrected through cartilage tissue remodeling, however, excessive articular step-off is associated with progressive deterioration of the articular cartilage, likely due to resulting supra-physiologic contact stresses on the more prominent areas. Abnormal contact stress is a key determinant of both cartilage repair and cartilage degeneration. A study of contact stress aberrations following imprecise reduction of simulated human cadaver tibial plateau fractures showed that, in general, peak local cartilage pressure increased with increasing step-off, but the results varied among specimens. In most specimens, cartilage pressure did not increase significantly until the fragment step-off exceeded 1.5 mm. However, in some specimens incongruities of as little as 0.25-mm caused peak local pressure elevations, suggesting that results may vary even among individuals with the same degree of articular incongruity. The degree of joint step-off that can be tolerated without causing long-term joint deterioration differs from joint to joint. A common “rule of thumb” is that residual step-off should not exceed the thickness of the articular cartilage at the injury site, but this rule almost certainly overstates the amount of step-off that can be accepted without consequence.

Loading and Motion: Prolonged immobilization of a joint following intra-articular fractures can lead to adhesion formation as well as deterioration of the cartilage, resulting in poor joint function. Early motion during the repair and remodeling phases of healing can decrease or prevent adhesions and the immobilization-induced deterioration of cartilage. However, animal experiments have shown that early joint loading can also increase inflammation and lead to cartilage degeneration. Cartilage repair tissue is particularly vulnerable to damage from excessive loading, so strict non-weight-bearing is typically maintained for at least 6 weeks. The role of continuous passive motion (CPM) remains a topic of debate, but its routine use after microfracture cartilage repair surgery and the results of some animal studies argues for its inclusion in the rehabilitation process after cartilage injury.

Patient Age: The long-term results of traumatically induced articular cartilage injury may also depend on the age of the patient. Recent studies have demonstrated age-specific differences in the response of chondrocytes to mechanical injury, with immature cartilage being much more susceptible to mechanical injury than mature cartilage. On the other hand, older age is often associated with poorer results after treatment of intra-articular fractures, possibly due to age-related alterations that decrease the capacity to repair injuries or withstand alterations in loading caused by joint incongruity.

**RESPONSE OF CARTILAGE TO MECHANICAL INJURY**

Cartilage damage associated with traumatic injuries is characterized by catastrophic disruption of cartilage matrix integrity and structure, extensive chondrocyte death in the area of cartilage injury, and expansion of this “zone of injury” which is facilitated by diffusible mediators such as nitric oxide. The initial damage can be worsened by persistent mechanical overload due to associated joint incongruity, instability, and/or limb malalignment. Chondrocytes in the superficial zone of articular cartilage are at particular risk. In vitro data show that the extent of cartilage damage is related to both the peak stress and strain rate. Injurious compression disrupts the collagen framework resulting in decreased load carrying capacity. Mechanical injury is also associated with proteoglycan loss, both from alterations to chondrocyte biosynthetic activity and from chondrocyte death. Mechanical overload causes chondrocytes to upregulate their expression of matrix degrading enzymes including ADAMTS family members and several MMPs, which may play a major role in subsequent cartilage degeneration.

**CONSEQUENCES OF CARTILAGE INJURY**

Clinical outcomes after cartilage injury depend on many factors including the size and location of the injury. Small lesions and/or lesions outside of the main weight-bearing areas of the hip, knee, and ankle often are well tolerated. However, this is not universally true, and small lesions often progress over time, particularly if there are associated injuries to other structures such as menisci or the stabilizing ligaments. Furthermore, cartilage injuries, with or without fractures, are risk factors for the development of osteoarthritis. Although the development of post-traumatic osteoarthritis is a complex, multifactorial process, there appears to be a clear relationship between the severity of the injury to the subchondral bone and subsequent joint degeneration. This relationship is best exemplified by recent studies that used CT data to estimate the energy absorbed in tibial pilon fractures, and then correlated that data with the subsequent development of ankle arthritis. There was 88% concordance of fracture energy and the development of arthritis, and linear regression analysis showed that fracture energy and articular comminution explained 70% of the variation in arthritis severity 2 years after injury.

**MODIFIERS OF CARTILAGE DAMAGE**

The acutely traumatized joint is a particularly hostile environment for articular cartilage, with the presence of multiple...
mediators of chondrocyte cell death, including: proinflammatory cytokines, reactive oxygen species, blood, and damaged matrix. Furthermore, surgical intervention poses additional risks of iatrogenic cartilage injury from mechanical damage associated with hardware insertion and cell death due to desiccation of exposed cartilage. Fortunately, some of these factors are easily addressed, while others are targets for emerging therapeutic approaches. At present, the most easily modified mediators of cartilage damage are joint hemorrhagic, which can be managed by evacuation and/or lavage, and cartilage desiccation, which is effectively managed by periodic rewetting of the joint surface intraoperatively.

**Summary**

The biology that underlies bone and cartilage healing involves complex processes. A basic understanding of these processes is essential to the rational treatment of fractures with a mind to optimizing the environment for uncomplicated healing. The main components essential to the healing of musculoskeletal tissues are: cells, ECM, bioactive molecule–receptor pairs, and blood supply. The cellular milieu is responsible for the creation of new tissues. ECM forms the scaffold on which these cells perform their synthetic function. Bioactive molecules allow communication between the various cell types described above. The blood supply provides fuel for this energy-intensive process. Thinking about the treatment of injuries with these components in mind will enhance the surgeon’s ability to promote healing and avoid complications during the treatment of their patients.

**References**

4. Alexander KA, Chang MK, Maylin ER, et al. Osteal macrophages promote in vivo during the treatment of their patients. surgeon’s ability to promote healing and avoid complications of injuries with these components in mind will enhance the this energy-intensive process. Thinking about the treatment of injuries with these components in mind will enhance the surgeon’s ability to promote healing and avoid complications during the treatment of their patients.

**Summary**

The biology that underlies bone and cartilage healing involves complex processes. A basic understanding of these processes is essential to the rational treatment of fractures with a mind to optimizing the environment for uncomplicated healing. The main components essential to the healing of musculoskeletal tissues are: cells, ECM, bioactive molecule–receptor pairs, and blood supply. The cellular milieu is responsible for the creation of new tissues. ECM forms the scaffold on which these cells perform their synthetic function. Bioactive molecules allow communication between the various cell types described above. The blood supply provides fuel for this energy-intensive process. Thinking about the treatment of injuries with these components in mind will enhance the surgeon’s ability to promote healing and avoid complications during the treatment of their patients.

**References**

4. Alexander KA, Chang MK, Maylin ER, et al. Osteal macrophages promote in vivo during the treatment of their patients. surgeon’s ability to promote healing and avoid complications of injuries with these components in mind will enhance the this energy-intensive process. Thinking about the treatment of injuries with these components in mind will enhance the surgeon’s ability to promote healing and avoid complications during the treatment of their patients.


