

# Bone and Bone Graft Healing

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Bone is unique in connective tissue healing because it heals entirely by cellular regeneration and the production of a mineral matrix rather than just collagen deposition known as scar. This article discusses the cellular, tissue, and organ levels in each of the following sections—skeletal embryology, normal bone, examples of abnormal bone, and bone graft healing—as they relate to the jaws and the craniofacial skeleton.

## **Pertinent embryology of the skull, facial bones, and jaws**

The calvarium, facial bones, clavicle, and jaws are intramembranous bones that arise from cells that migrated from the neural crest adjacent to the notochord. These bones develop, grow, and heal by direct ossification of mesenchyme rather than from preformed cartilage. By contrast, all the other bones of the skeleton, which are referred to as the appendicular skeleton, arise from preformed cartilage by the process known as endochondral ossification. Specifically, the calvarium originates as six membrane-covered neural crest cell islands that correspond to the bilateral frontal bone segments, the bilateral parietal bone segments, and the midline occipital squamous plate and occipital bone proper separated by fontanelles [1]. The anterior fontanelle closes at approximately 1.5 years of age and becomes known as the midsagittal suture. The maxilla as well as the incus and mandible arise separately from the first pharyngeal arch. Although each arises with a central cartilage element, which in the maxilla is called the palatopterygoquadrate bar and in the mandible is called Meckle's cartilage, the cartilage

itself does not transform into bone but only serves as a scaffold on which neural crest mesenchyme transforms into bone. These cartilages involute before birth. The bones of the calvarium, facial bones, jaws, and even the clavicle have been referred to as “ectomesenchymal bone” and are thought to be embryologically similar. Bone morphogenetic protein-4 (BMP-4) also is thought to play the major role in neural crest migration orientation and actual bone morphogenesis, whereas BMP-2 plays a major role in neural crest ventralization toward the jaws and away from the calvarium but less of a role in actual bone development [2].

The conjectured and unproven importance of this embryology is that bone grafts from the calvarium are ideally suited for midface and jaw reconstruction where feasible because they are similar ectomesenchymal bones. This is reinforced by the frequent observation that calvarial block onlay grafts to the midface and jaws experience less resorption than do grafts from endochondral bones, such as the ilium or ribs. The disease of myositis ossificans also has been shown to relate to muscles that overexpress receptors for BMP-4 [2]. It has also been suggested that a recombinant human BMP-4 may be the most ideal recombinant BMP for jaw and facial bone reconstruction.

## **Bone as a tissue**

Bone is fundamentally composed of cells, inorganic matrix, and organic matrix. The cells are hematopoietic (blood forming) and nonhematopoietic (non-blood forming) stem cells in the bone marrow, osteoblasts (of which some are endosteal osteoblasts that line the trabecular bone between the cortices (Fig. 1) and others

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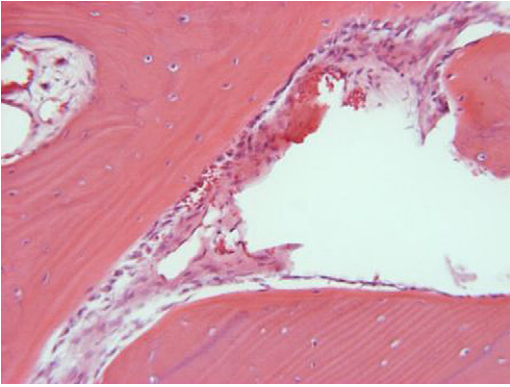


Fig. 1. Endosteal osteoblasts lining trabecular bone.

that line the inner surface of each cortex), and some other osteoblasts that comprise the inner or cambium layer of the periosteum (Fig. 2). Osteocytes, which are mature osteoblasts encased in a mineral matrix, and osteoclasts, which resorb bone upon stimulation and begin the bone renewal process, which is often termed “bone turnover” or “bone remodeling,” are the remaining bone cells (Fig. 3). The inorganic matrix and organic matrix are combined. The basic organic component is type 1 collagen, which comprises 98.5% of the noncellular organic matrix. The inorganic matrix is nearly all hydroxyapatite. Essentially, bone matrix is mostly type 1 collagen laced with crystals of hydroxyapatite. However, there are several important noncollagen proteins in bone, namely BMP, insulin-like growth factors-1 and -2 (IGF-1 and IGF-2), sialoprotein, and osteopontin.

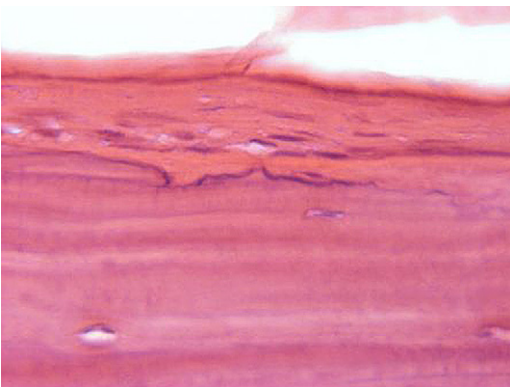


Fig. 2. Periosteum with several cell layers of osteoblasts. The inner-most layer is known as the cambium layer.

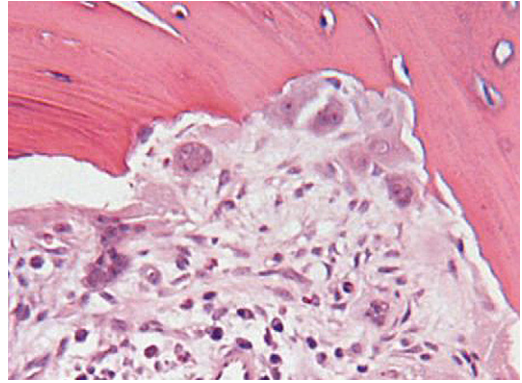


Fig. 3. Osteocytes are seen here in their lacunae. Osteoclasts are resorbing bone as multinucleated giant cells.

The evolutionary purpose of bone as a tissue and the skeleton as a whole is internal structural integrity, an attachment for muscles, a reservoir for hematopoietic and mesenchymal stem cells, and a main regulator of serum calcium for skeletal and cardiac muscle contraction and therefore locomotion and organ perfusion.

### Bone renewal (remodeling)

The biochemistry of bone as a tissue can best be explained in the context of bone cell interactions starting with existing bone. Bone is normally inhibited from resorption by osteoprotegerin (OPG), which is a protein secreted by osteoblasts to regulate the rate of resorption as an inhibitory signal to the osteoclast (Fig. 4) [3]. As the osteoblast matures into an osteocyte it gradually loses its ability to secrete OPG and becomes vulnerable to normal osteoclastic resorption. Therefore, old bone, injured bone, and dead bone become resorbed.

Osteoclasts arise from mononuclear precursor cells of the macrophage lineage in bone marrow [4]. They mature rapidly under the stimulation of macrophage colony stimulating factor and interleukin-1 and -6 (IL-1 and IL-6) and are then extruded into the circulation as quiescent nonresorbing osteoclasts because of the inhibiting influence of circulating calcitonin (Fig. 5). The osteoclast only begins active bone resorption in response to the overriding signal of circulating parathyroid hormone and locally secreted receptor activator nuclear kappa-b ligand (RANKL) [5,6]. RANKL binds to RANK receptors on the osteoclast cell membrane to initiate resorption [7]. Although RANKL is known to be secreted

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