

## BONE DEVELOPMENT AND ITS RELATION TO FRACTURE REPAIR

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**Bone formation** is complex but the three-dimensional positioning of cells and matrices is straightforward. Normal bone develops using only 2 mechanisms. **Intramembranous bone formation** is mediated by the inner periosteal osteogenic layer with bone synthesized directly without the mediation of a cartilage phase. **Endochondral bone formation** describes the synthesis of bone on a mineralized cartilage scaffold after epiphyseal and physeal cartilage have shaped and elongated the developing organ. In bone tissue formation osteoblasts synthesize and deposit type I collagen, the main protein constituent of bone matrix, in only 2 basic conformations, **woven and lamellar**, processes repeated in normal bone development, in bone repair utilizing any of several mechanisms, and in several pathologic conditions. We introduce a specific terminology for osteoblasts describing them as either **mesenchymal osteoblasts (MOBL)** or **surface osteoblasts (SOBL)** since these 2 variants only are seen to underlie essentially all bone tissue formation. Matrix conformation shift from woven to lamellar is virtually always abrupt with infrequent tendency to shading of one pattern into the other via fibro-osseous or chondro-osseous accumulations. With the first stages of bone formation, in an environment where no pre-existing bone matrix is present, undifferentiated mesenchymal cells differentiate to pre-osteoblasts and then to osteoblasts which secrete collagen fibrils in a 360 degree direction in random pericellular array. We refer to these cells as **mesenchymal osteoblasts** and the bone matrix synthesized as **woven**. When a sufficient amount of woven bone has been synthesized to serve as a **structural scaffold**, osteoblasts which we refer to as **surface osteoblasts** i)array themselves in well-polarized fashion only along the woven bone surface, ii)secrete collagen fibrils only onto the bone surface (not circumferentially), and iii)those fibrils are in a parallel or **lamellar** orientation. An osteoblast completely surrounded by the

mineralized collagen matrix is now an **osteocyte**, although it can be in woven or lamellar bone.

**Bone repair** can occur by different but specific mechanisms primarily dependent on the biophysical environment. Although the various types of repair use differing normal cells and tissues, the eventual bone synthesis is always mediated by the mesenchymal and/or surface osteoblasts (MOBL and SOBL) and via the woven and/or lamellar matrix conformations. The histologic patterns of bone repair are: i) **endochondral bone repair** (repair by callus formation), mediated by inner periosteal layer and marrow tissues, synthesizing cartilage and then woven and lamellar bone in an environment of interfragmentary space and mobility; ii) **primary bone repair** (contact repair), mediated exclusively by intraosseous haversian system osteoblasts (SOBL), without a cartilage phase, synthesizing lamellar bone initially parallel to the longitudinal axis of the bone in an environment of no interfragmentary space and rigid stability; iii) **direct bone repair** (gap repair, direct transformational bone repair) mediated without a cartilage phase by marrow derived vessels and mesenchymal cells, initially perpendicular to the long axis of the bone (woven and lamellar) and then restructured along the long axis (lamellar), in an environment of interfragmentary space > 0.1 mm wide but with rigid stability; and iv) **distraction osteogenesis** (callotasis) mediated by inner layer periosteal and marrow tissue, synthesizing woven and then lamellar bone in the slowly widening gap, parallel to the long axis of the bone in an environment of stability and slow distraction.

Our work demonstrates the repetitive finding of woven to lamellar bone formation by MOBL and SOBL cells in developing and repair bone. A cell area/total area ratio of certain dimensions appears to **signal** that sufficient woven scaffold has been deposited to switch matrix deposition to a lamellar form, an assembly mechanism that is dependent on cells and biophysical forces.