Skeletal biology: Where matrix meets mineral

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Abstract

The skeleton is unique from all other tissues in the body because of its ability to mineralize. The incorporation of mineral into bones and teeth is essential to give them strength and structure for body support and function. For years, researchers have wondered how mineralized tissues form and repair. A major focus in this context has been on the role of the extracellular matrix, which harbors key regulators of the mineralization process. In this introductory minireview, we will review some key concepts of matrix biology as it related to mineralized tissues. Concurrently, we will highlight the subject of this special issue covering many aspects of mineralized tissues, including bones and teeth and their associated structures cartilage and tendon. Areas of emphasis are on the generation and analysis of new animal models with permutations of matrix components as well as the development of new approaches for tissue engineering for repair of damaged hard tissue. In assembling key topics on mineralized tissues written by leaders in our field, we hope the reader will get a broad view of the topic and all of its fascinating complexities.

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Introduction

What is mineralized tissue?

Mineralized tissues come in many "shapes and forms" that are depicted schematically in Fig. 1. There are five types of bones that include 1) flat bones that protect internal organs such as the skull shown in Fig. 1, 2) long bones that support weight and facilitate movement with the femur being one example, 3) short bones that are cube shaped and found in wrists and ankles, 4) irregular bones with complex shapes such as the vertebrae and 5) sesamoid bones that are embedded in tendon tissue. Like bone, the tooth is highly mineralized and contains many of the same matrix components, but despite this fact it is very different from bone, as can be seen in Fig. 1. The outer enamel layer of the tooth is "super mineralized", making it the hardest tissue in the body. Its unique composition gives it astounding strength that protects the tooth from "wear and tear" during eating and chewing. This special issue of *Matrix Biology* is as diverse as the skeleton itself, with a combination of primary research articles submitted to the journal, along with reviews describing the composition and ultrastructure of matrix proteins and their role in regulating cell and tissue function. The issue is divided into four chapters that describe the importance of matrix in 1) bones, 2) teeth, 3) tendon, cartilage and cancer and 4) in tissue engineering.

Bones

Type I collagen

At least 27 different collagen types have been identified so far [1], many of which are found in the skeleton. The most abundant species in mineralized tissue is Type I collagen, long known to have vital roles in regulating skeletal integrity. The production and processing of collagen are highly orchestrated [1] involving a multitude of chaperones and enzymes that modify and crosslink collagen during its assembly into a triple helix and ultimately into fibrils [2]. Our issue begins with an in-depth overview by P. Trackman, of

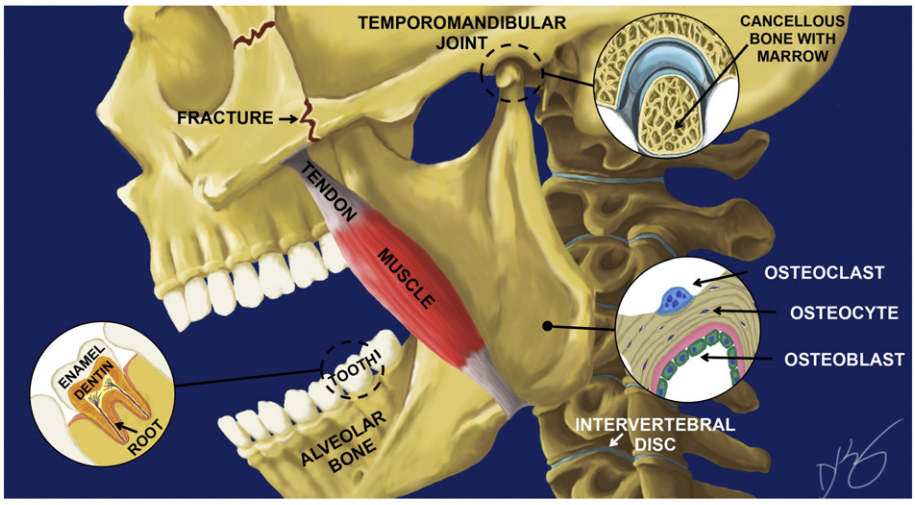

Fig. 1. Schematic of a skull depicting key mineralized tissues including a tooth with enamel, dentin and roots, masseter tendon, alveolar bone in the jaw, the temporomandibular joint (TMJ), and the intervertebral disc (IVD). Key cell components of bone are shown in the lower right corner that include the multinuclear osteoclast (blue), the osteocyte (black) and the osteoblast (green). Commonly fractured bones in the face are shown as zigzag lines behind and below the eye socket in the zygomatic arch. Illustration is by David Kirby, co-first author, on the paper in this special edition by Myren et al.

enzyme-dependent collagen crosslinking with a focus on lysyl oxidases (LOX). The LOX family is composed of 5 members that include LOX, and the lysyl oxidase-like enzymes LOXL1–LOXL4. The review tells us what is currently known about the biochemical reactions dependent on LOX and, further, the consequences to bone tissue formation when these enzymes are depleted. The multiple cell and molecular functions of LOX members beyond collagen cross-linking are discussed including their potential role in osteogenic differentiation, angiogenesis and in bone healing.

It is generally believed that collagen orients proteins that serve as a nidus for minerals to localize and accumulate, therefore serving a key function in mineralized tissues [3]. Testimony of the importance of type I collagen in mineralized tissue formation comes from patients with mutations in the type I collagen gene (referred to as the Col1A1 and Col1A2 genes), who are afflicted with severe skeletal deformities in a condition known as osteogenesis imperfecta (OI, or brittle bone disease) [4]. Interestingly, many lethal mutations in OI are located in the triple helical domain of collagen in a region that aligns with binding sites for other ECM components [5] including proteoglycans [6]. This finding emphasizes the importance of the potential synergy between ECM components where one ECM member can affect the function of another [7]. Further studies are needed to delineate the ECM interplay in this mineralized tissue disease.

One of the current treatments for OI is bisphosphonates, and while bisphospohnates have proven effective in reducing fracture rates they do not completely eliminate them [8]. The paper by Berman et al. used a mouse model of OI known as OIM with a frameshift mutation in the Col1a2 gene of alpha2 chain of type I collagen to ask the question: could the selective estrogen receptor modulator (SERM), rolaxifene, be a novel treatment for OI and, if so, how would it work? Their study showed that rolaxifene increased the mechanical properties of bone when tested both *in vivo* and *ex vivo*, providing a foundation for the development of new therapies using this SERM to reduce bone fragility in patients with OI. A second paper in this issue by Mertz et al. used a different OI mouse model with a Gly610Cys mutation in the alpha 2 chain of type I collagen to show how this mutation disrupts bone modeling mineralization and overall bone toughness. Such studies are needed to understand the tissue and cell basis for the mineralized tissue abnormalities observed in OI.

Non-collagenous proteins and proteoglycans

The importance of collagen in bone mineralization presents a conundrum: how do tissues that do not make collagen (like enamel) control the mineralization process? In this context, it must further be questioned: why does skin that is rife with type I collagen not mineralize? There must be extracellular matrix components other than collagen that are involved in regulating the mineralization of hard tissues. To address some of these points, a review by Boskey et al. describes the mineralization process and its relationship to a family of proteins called Small Integrin-Binding Ligand N-linked Glycoproteins (SIBLINGs). A biochemical characteristic of the SIBLINGs is that they are highly acidic, which is likely one reason they have affinity for the basic hydroxypapatite that makes up the mineral composition of bone. What is interesting about the SIBLINGs is that they are intrinsically “disordered”, meaning that they