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Review

Mechanistic and therapeutic insights gained from studying rare skeletal diseases

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ABSTRACT

Rare bone diseases account for 5% of all birth defects and can cause significant morbidity throughout patients' lives. Significant progress is being made to elucidate the pathophysiological mechanisms underlying these diseases. This paper summarizes presentation highlights of a workshop on Rare Skeletal Diseases convened to explore how the study of rare diseases has influenced the field's understanding of bone anabolism and catabolism and directed the search for new therapies benefiting patients with rare conditions as well as patients with common skeletal disorders.

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Introduction

Genetic bone diseases are an important cause of disability in the US and remain difficult to diagnose and treat owing to variability in disease

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expression and symptom severity [1]. The interconnection between the different components of bone—cells, vasculature, and matrix—makes it challenging to dissect the biological mechanisms affected by these rare disorders. New methods for imaging the skeleton, performing massively parallel sequencing of DNA and RNA, creating animal models of human skeletal disease, and studying the consequences of mutation at the single cell level, have facilitated our understanding of fundamental mechanisms responsible for skeletal growth and homeostasis. Many new discoveries that are relevant to persons affected by common skeletal disorders such as osteoporosis and osteoarthritis have their origins in the study of patients with rare bone diseases. Thus, studying rare skeletal diseases has improved our understanding of skeletal biology and contributed to the development of new approaches for improving bone health.

This manuscript summarizes twelve lectures delivered by invited speakers at an NIH-supported workshop on Rare Bone Diseases held on September 11, 2014, in Houston, TX, and attended by more than 250 clinicians and scientists.

The nosology of rare bone diseases — Krakow

Dr. Deborah Krakow provided examples of clinical, radiologic, and biochemical characterizations of rare skeletal diseases facilitating the discovery of pathways and processes involved in skeletal patterning, growth, and homeostasis.

Heritable skeletal disorders form a heterogeneous group of more than 450 well-defined diseases, resultant from mutations in more than 200 genes. Initial attempts at classification relied primarily on radiographic and clinical findings and distinguished between skeletal dysplasias, a general condition affecting bone and cartilage, and dysostoses, a disorder manifested by abnormalities in an individual or group of bones [2]. Despite variability in the clinical manifestations and severity of these pathological states, significant phenotypic overlap posed a challenge in disease recognition and risk assessment, creating the need for a comprehensive, systematic classification that could guide diagnosis.

Spranger first proposed the concept of 'bone families' in the 1980s as disorders with common phenotypic, radiographic, and histologic features sharing the same underlying pathophysiological mechanisms and/or molecular pathways [3]. With the advent of molecular biology, diseases once thought to be distinct entities are now grouped according to the gene(s) and pathway(s) affected. For example, mutations in filamin A account for conditions displaying wide variability such as Melnick–Needles syndrome, otopalatodigital syndromes and frontometaphyseal dysplasia [2]. By contrast, similar clinical features may be due to mutations in different genes, as in the case of the multiple epiphyseal dysplasia group of diseases, associated with defects in cartilage oligomeric matrix protein, collagen type IX, and matrilin 3, all thought to similarly participate in the assembly of the extracellular matrix (ECM) [2]. Polygenic disease entities may in fact share the same mechanistic basis. Osteogenesis imperfecta (OI), for instance, is attributed to the action of several dysfunctional proteins, previously deemed unrelated and now recognized to be involved in common processes in mineralization and signaling in the matrix. The study of OI has allowed biologists to identify interactions between gene products that would have never been predicted. Further, new pathological components have been identified as a result of recognizing that a gene associated with a specific bone disorder is also responsible for symptoms affecting other organs and systems. Gain-of-function mutations in transient receptor potential cation channel subfamily V member 4 (TRPV4), a calcium channel, result in distinctive phenotypes: mild brachyolmia, spondylometaphyseal dysplasia, Kozlowski type, and the more severe metatropic dysplasia [2]. Notably, Charcot–Marie–Tooth disease type 2C is also caused by defects in this receptor [4], an observation that led to the identification of a pathological neuromuscular component in the TRPV4 family of disorders [5].

The most recent revision of the Nosology and Classification of Genetic Skeletal Disorders combines pathological, histologic, and biochemical information, as well as molecular and developmental aspects, to categorize recognized disease entities into 40 distinct groups [2]. The disease classification scheme goes beyond its role in assisting diagnosis and informing treatment and counseling, by suggesting links between molecules and pathways. Serpentine fibula-polycystic kidney syndrome, thought to be a filamin-related disorder based on clinical and radiographic phenotype, clearly illustrates this concept. However serpentine fibula-polycystic kidney syndrome and the rare Hajdu–Cheney syndrome are caused by truncating mutations in neurogenic locus notch homolog 2 (NOTCH2) [6]. This raises the interesting hypothesis of filamin involvement in the NOTCH signaling pathway.

The classification of rare bone diseases has undoubtedly delineated important elements of normal and diseased bone physiology and contributed to improved diagnosis. In the age of molecular medicine, and despite some unsolved entities, nosological schemes enable clinicians to quickly recognize signs and symptoms, establish otherwise unforeseen mechanistic relationships, and potentially identify new therapeutic targets.

Skeletal elements affected in rare bone disorders

Drs. Lynda Bonewald, Stuart Ralston, Maurizio Pacifici, Bjorn Olsen, and Brendan Lee gave examples of rare bone diseases yielding insights about independent and coordinated functions of bone cells, vasculature, and matrix on skeletal health.

Osteoblasts and osteocytes — Bonewald

Osteoblasts have a vital role in bone homeostasis and undergo a tightly regulated differentiation process. Runt-related transcription factor 2 (RUNX2) is an early mediator of osteoblast specification and direct regulator of OSTERIX (OSX), a member of the Sp zinc-finger transcription factor family that further specifies the osteoblastic lineage [7]. Deficiencies in osteoblast-specific proteins such as type I collagen and tissue non-specific alkaline phosphatase (TNSALP) have been associated with OI and hypophosphatasia, respectively [2]. Osteocytes, which constitute over 95% of all bone cells in the adult skeleton, originate from the terminal differentiation of osteoid-producing osteoblasts that become embedded in the bone matrix. They have endocrine and mechanosensory functions in bone remodeling and are able to establish and direct communication between themselves and the bone surface by extending and retracting their cellular processes into the bone marrow and vascular spaces. Osteocytes also regulate osteoclasts through receptor activator of nuclear factor kappa-B (NFκB) ligand (RANKL) and produce osteoblast-modulating factors such as sclerostin, encoded by the sclerostin gene (*SOST*) [8]. Deleterious mutations in SOST, a strong inhibitor of bone formation responsive to mechanical load via the wingless-related integration site (Wnt)/β-catenin signaling pathway, result in sclerosing bone syndromes, whereas activating mutations in fibroblast growth factor 23 (FGF23), also highly expressed in osteocytes, cause autosomal dominant hypophosphatemic rickets [2]. Autosomal recessive hypophosphatemic rickets is due to defects in dentin matrix acidic phosphoprotein 1 (DMP1), and a sex-linked form of the disease is caused by mutations in phosphate-regulating neutral endopeptidase on chromosome X (PHEX) [9]. DMP1 and PHEX downregulate FGF23 signaling, which is actively involved in the systemic regulation of phosphate metabolism, essential for bone mineralization [10]. Elevated levels of circulating FGF23 also exert pathological effects in the heart by inducing vascular calcification in patients with chronic kidney disease [11].

Although therapeutic approaches to bone disease have traditionally focused on osteoblasts, current research supports the use of agents targeting osteocyte-specific proteins such as sclerostin. Anti-sclerostin antibodies reduce bone loss and promote fracture healing in animal