A Molecular View of Skeletal Dysplasia

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Abstract
The skeletal dysplasia forms a large group of hereditary disorders characterized by abnormal growth and malformations of bone and cartilage. The clinical severity ranges from mildly affected short stature to lethal forms. Clinical examination, biochemical testing and imaging had been used for diagnosis for long. Emerging molecular investigation has provided a new platform to accurately diagnose skeletal dysplasia. Etiopathogenesis of skeletal dysplasia is better documented now, with rapid accumulation of knowledge concerning defective genes and proteins causing this group of disorders. Mutations responsible for skeletal dysplasia may cause defects in the synthesis of structural proteins and in metabolic pathways, degradation of macromolecules, growth factors and receptors and transcription factors. In this review, we briefly discussed skeletogenesis and pathogenesis of skeletal dysplasia

***Keyword**: skeletogenesis, skeletal dysplasia,*

1. Introduction

Skeletal dysplasia (SD) are a genetically heterogeneous group of disorders affecting the development of chondro-osseous tissues and leading to abnormalities in the size and shape of various segments of the skeleton(1). This process is additionally complicated by the rarity of the individual conditions The internationally recognized classification system currently places 372 different conditions into 37 groups defined by molecular, biochemical and/or radiographic criteria(2,3). Although pathogenic and molecular criteria have been integrated for classification purposes, SD are still identified by clinical features and imaging appearance. Although individual skeletal disorders are rare, collectively the prevalence of SD recognized at birth likely ranges between 2.3 and 3.2/10,000 births(4), and they account for a significant number of newborns with genetic disorders(5) . The most common SD at birth were achondroplasia (0.5 and 1.5/10,000 births), thanatophoric dysplasia, achondrogenesis (0.2–0.5/10,000 births), and osteogenesis imperfecta (0.4/10,000 births) (5). During pregnancy, the most commonly defined SD were osteogenesis imperfecta type II, thanatophoric dysplasia and achondrogenesis type II. (6). Precise prenatal diagnosis of the specific SD allows accurate counseling with respect to perinatal lethality, consideration for focused molecular analysis, prediction of neonatal complications, recurrence risk and maternal management(6). The establishment of a precise diagnosis is important for numerous reasons including prediction of adult height, accurate recurrence risk, prenatal diagnosis in future pregnancies and most importantly for proper clinical treatment. When a patient is referred for genetic evaluation of suspected skeletal dysplasia, clinical and radiographic indicators and more specific biochemical and molecular tests are used to try to arrive at the underlying diagnosis. Preferably, the clinical features and pattern of radiographic abnormalities are used to generate a differential diagnosis so that the appropriate confirmatory tests can be done

The fetal skeleton is relatively well visualized by ultrasound (US) during the routine morphology scan so that SD with prenatal onset, especially those severe disorders with pronounced shortening of long bones, is often suspected. However, given the large variety and complexity of these anomalies, antenatal diagnosis of the specific disorder remains difficult(7). Although the potential advantages of 2-dimensional ultrasound (2D-US), 3-dimensional ultrasound (3D-US) and postnatal radiological and autopsy evaluations have been postulated, none performs as effectively as molecular analysis. We shall evaluate the contribution of molecular analysis to the prenatal diagnosis of SD in patients where

US, biochemical, radiological and clinical made a provisional diagnosis to the disorder concerned.

For a better understanding of skeletal dysplasia, one should understand the basic behind bone formation, maturation and differentiation and from there one can understand how mutation at gene level would lead to a particular phenotype. Molecular understanding of the pathways and gene involved is therefore fundamental in medicine (8). Once we understand this, we can classify bone dysplasia based on the mutation involved, single gene or multiple genes, its hereditary capability, recurrence risk, lethality and its penetrance thought generation. The original classification of skeletal dysplasia was simple but grossly inaccurate. Patients were categorized as either short-trunked (Morquio syndrome) or short-limbed (achondroplasia) (9). As the field expanded to over 400 different dysplasia described, this gave rise complicated nomenclature (9-11). The advent of molecular testing has allowed the grouping of some dysplasia into families and a small trimming of numbers. In this review, we consider the basic of skeletogenesis and etiopathogenesis of skeletal dysplasia.

2. Skeletogenesis

Bone is a specialized type of connective tissue, which is composed of cells, vessels and extra cellular matrix components which become mineralized with calcium salts in the form of hydroxyapatite. The bones also are covered with a thin layer of connective tissue called the periosteum and the ends of long bones are covered by articular cartilage. The external or periosteal surface of the bone is fibrous and functions as an anchor for the attachment of muscles, tendons and ligaments. Some bones (in adults is found only in the vertebrae, hips, breastbone, ribs, skull and at the ends) contain hematopoietic tissue in the bone marrow space. Bones are composed of an outer shell of cortical (compact) bone, which surrounds a network of trabecular (plates) or cancellous bone(12). Cortical bone is dense, and accounts for 80% of the total bone mass in the adult skeleton. Cortical bone is most abundant in the shafts of long bones. It has a slow turnover rate, when compared with trabecular bone and a high resistance to bending and torsion. Cortical bone is composed of structures called osteons or Haversian systems. Each osteon consist of a central canal, containing vessels, nerves and possibly lymphatics. Osteons consist of concentric layers of mineralized bone. Trabecular bone, consists of rod-and plate-like elements; joined together to form a spongy structure, which contains space for vessels and bone marrow. Trabecular bone is most abundant in vertebrae, pelvis, flat bones and the ends of the long bones. Trabecular bone accounts for the remaining 20% of the total bone mass in adults, but contains nearly ten times the surface of the compact bone. The vertebrate skeleton derives from three distinct embryonic lineages**.** Undifferentiated descendants of these lineages migrate and/or proliferate to sites in the embryo where skeletal elements will. Development processes involved in the skeletal patterning and bone formation(13) develop. The location of the initial skeletal formation will determine which one of these three mesenchymal cell-lineages contributes to particular bones and cartilage of the future skeleton. Cranial neural crest cells migrate from the branchial arches to the craniofacial skeleton, the axial skeleton derives from the paraxial mesoderm (somite) and the limb skeleton is the product of lateral plate mesodermal cells

Later on several morphogenic transformations will occur to form the mature skeleton, called **skeletogenesis**. In general, the skeletal morphogenesis can be divided into two major phases. During the first phase, the following pattern formation of the general body plan (trunk, head and appendices), characteristic mesenchymal condensation of high cell density will be formed. These condensation outline the pattern of the future bones, referred to as **skeletal patterning**. This morphogenesis is under the control of several major signaling pathways. Precisely adjusted cell fate determination, proliferation and differentiation/ maturation will follow these early patterning events. Early patterning mechanism defines the places where future bones will be formed within mesenchymal condensation. Although the intramembranous ossification is different from that of the endochondrial, the participating osteoblasts in these two processes share morphological identity.

This suggests common pathways and regulation of the osteochondral progenitors in these two mechanisms of bone formation. **Sox9** and **RUNX2** transcription factors are the first currently known molecular markers that are required for chondrocyte and osteoblast cell fate determination(8,14). The initiation of the expression is coordinated such that the Sox 9 activity precedes that of RUNX2. The Sox9 effects are further enhanced by two other members of the Sox family, **Sox5** and **Sox6** (15). In addition to the Sox9 and RUNX 2 function, Wnt, Ihh, Bmp and Fgf signaling pathways are also incorporated within the process of cartilage and bone formation. Thus the enhanced Wnt signaling results in an increased bone formation and RUNX 2 expression by decreasing the Sox9 levels(16) and the chondrogenic differentiation potential of the bi-potential osteochondral progenitors the endochondral bone formation but does not affect the fate of the mesenchymal progenitor cells.

The Bmp signaling promotes the osteochondral progenitor differentiation to both chondrocytes and osteoblasts via two currently known pathways. The first one (canonical Smad-mediated) exploits Bmp type II and I receptors (BmpRII, BmpRIA, BmpRIB and Alk2) to activate Bmp-receptor regulated Smads (R-Smads) Smad1, Smad2 and Smad8. In the second (non-canonical) pathway, Bmp activate consecutively Tak1 and p38 Mapks. In addition the Bmp chondro- and osteogenic functions are modulated by inhibitors Noggin, Chording and Grem1. The importance of the Fgf ligands and their receptors in osteogenesis was elucidated by discovery that several chondrodysplasias/ dysostoses in humans are caused by mutations in **FGFR1, FGFR2** and **FGFR3 (17)**. However, there is no doubt about their importance in this process, at least during intramembranous bone formation, since FGFR1, FGFR2 and FGFR3 mutations cause **craniosynostosis**. Depending on the cell, the Fgfs have a dual function concerning the osteoblast proliferation and differentiation. Bone in the adult skeleton is constantly being renewed and repaired in response to a variety of stimuli, through the process of bone remodeling which can be divided into four stages, **resorption, reversal, formation and quiescence**. During the resorption phase, osteoclast precursors are recruited to a specific resorption site where they differentiate to form mature osteoclasts. Following retraction of the bone-lining cells, osteoclasts attach to the bone surface by forming a sealing zone and create a greatly invaginated secretory surface called the ruffled border. The ruffled border creates an acidic and proteolytic environment which results in an active bone resorption site in the enclosed space, called a resorption pit or Howship's Lacuna. After osteoclasts have resorbed bone, there is a reversal phase during which the osteoclast undergoes apoptosis. Osteoblast precursors are attracted to the resorption pit, where they differentiate into mature osteoblast and secrete and deposit bone matrix. As bone formation proceeds, some osteoblast become embedded in the bone matrix and differentiate to osteocytes. Following bone formation, the osteoid is slowly mineralized to form mature bone. This is followed by a period of quiescence. Under normal conditions the amount of bone removed by osteoclasts exactly equals the amount of bone formed by osteoblast. Any imbalance in the regulation of bone remodeling results in bone disorder.

3. Pathogenesis of skeletal dysplasia

Mutation of early patterning genes, which regulated the skeletogenesis, causes disorders called **dysostoses**. These are most frequently cell-to-cell signaling molecules and transcription factors regulating cell migration, proliferation and fate determination events. The disturbed gene function(s) affect(s) only specific skeletal elements, whilst the rest of the bones may remain unaffected. A primary target of the abrogated morphogenesis could be all three major divisions of the vertebrate skeleton: craniofacial, axial and appendicular. However, genes/pathways active during the skeletal patterning are also involved in other morphogenic/ organogenic events so that, when mutated, the resulting skeletal defects are part of a syndrome which may include anomalies of non-skeletal tissues. This phenotypic phenomenon is known as **pleiotropy** and studying different forms of dysostoses has helped to obtain important insights in skeletogenesis.

In contrasts, mutations in genes that are involved mainly in organogenesis cause disorders called **osteochondrodysplasias**. In this group, the development and growth of most skeletal elements are affected in a generalized fashion. In addition, the cartilage and bone formation includes the synthesis of specialized extracellular matrices, which play a crucial role in the developing bones. This can be seen for example in skeletal dysplasia resulting from mutation in matrix molecules (**collagen types I, II, IX, X, XI**, agrecan and perlecan). Finally, many genes play an important role in both the skeletal morphogenesis (patterning) and organogenesis (cartilage and bone formation) and as a consequence some inherited bone disorders can display both features of both dysostoses and chondrodysplasias. For example **Cleidocranial dysplasia** is caused by **RUNX2** mutation(18), ***HOX*** gene mutation causes synpolydactyly and Campomelic dysplasia caused by haploinsufficiency of the transcription factor **SOX9**. Bone deformities may range from not affecting daily activities to being lethal. For example, the Type II collagenopathies range from the precocious osteoarthritis to perinatal lethal form (Achondrogenesis Type II) (19-22). This also was the first group of skeletal dysplasia for which the underlying genetic defect was found(23). That say, spectrum of skeletal dysplasia ranges from individuals with normal stature and survival but early onset osteoarthrosis to the perinatal lethal form(11). We can argue that one gene mutation is enough to affect one or multiple important pathways in born formation and the resulting deformities may have a range of outcome or expression in phenotype. So it is important to recognize them early in childhood or during prenatal period.

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