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Glycobiology and the Growth Plate: Current Concepts in Multiple Hereditary Exostoses

Kevin B. Jones, MD

Department of Orthopaedic Surgery, Center for Children's Cancer Research, Huntsman Cancer Institute, Primary Children's Medical Center, University of Utah, Salt Lake City, Utah

Abstract

Background—Multiple Hereditary Exostoses, also termed Multiple Osteochondromas, is a heritable disorder of connective tissue with primarily orthopaedic clinical manifestations. Understanding of its biological underpinnings has been advanced on a variety of fronts in recent years.

Methods—The multi-faceted literature regarding osteochondromagenesis as well as the major clinical challenges in patients with multiple osteochondromas were reviewed.

Results—Consideration of recent advances in molecular biology, biochemistry, and animal modeling of osteochondroma pathogenesis yields a unified model.

Conclusions—Mechanistic details and therapeutic targets have yet to be elucidated, but the general biology of osteochondroma formation is increasingly clear, as well as its implications in the orthopaedic clinical setting.

Introduction

Multiple hereditary exostoses (MHE), also called multiple osteochondromas (MO), and previously called diaphyseal aclasis, is a condition with an autosomal dominant inheritance pattern. This disease remains, at this point, primarily an orthopaedic disease, in terms of its clinical importance, but its biology spans many fields of science. It is characterized by multiple cartilage-capped bony protuberances, called osteochondromas, or exostoses, projecting from the metaphyses of long bones[1]. Patients also variably exhibit slightly shortened stature, with limbs disproportionately short compared to the spine. The bony growths and bone-length growth disturbances present a variety of orthopaedic challenges. One further clinical challenge presented by this disease is malignant degeneration of an osteochondroma into a secondary chondrosarcoma. Although malignant degeneration is very rare, even among patients with many osteochondromas all over the skeleton, osteochondromas still represent one of extremely few pre-malignant lesions related to sarcomagenesis.

Since the first case of MHE/MO was reported in 1814, nearly one thousand scientific articles have been published related to it. In the last year, the publication of a few critical articles and additional information synergized at the Third International MHE Research Conference make now an ideal time to update the orthopaedic physicians primarily serving

Address Correspondence to: Kevin B. Jones, MD, 2000 Circle of Hope Drive, Room 4263, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112, Phone: 801-585-0300, Fax: 801-585-7084, kevin.jones@hci.utah.edu.

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patients with this disease with the latest related science from biochemistry all the way through population-based studies.

Biochemistry

The mutations known to cause multiple hereditary exostoses (MHE), are localized to two genes, *EXT1* and *EXT2* in humans. The precise function of these genes, catalytically, is not entirely understood, but it is understood that these are involved in a heterooligomeric complex in the Golgi apparatus of most human cells (Figure 1). There, they participate in heparan sulfate chain elongation[2-3]. Heparan sulfate is one type of sugar chain that can be added to specific proteins headed for the cell surface and extra cellular matrix. As all biological reactions at the cell surface and otherwise depend on chemistry, and chemical functionality depends on the physical shape of the interacting entities, glycobiology plays a powerful role in determining the functionality of all entities in the extracellular space, where sugar moieties of some variety or another coat nearly all exposed surfaces of proteins. As exposed protein surfaces are covered with sugar chains, their physical shapes, whose interactions define their biology, are derived as much from these post-translational sugar modifications as they are from the amino acid sequence itself.

Great strides forward have been made in the study of the structure-activity relationships of glycosaminoglycans. As with the study of nearly every other type of molecule, the study of biologically functional sugars is getting broader and deeper with the assistance of array type technologies[4-7]. Such glycomics efforts can screen and sequence large libraries of oligosaccharides simultaneously[8]. Heparan sulfate (HS) is highlighted as an important specific oligosaccharide on the cell surface and in the extracellular matrix.

Mouse embryonic stem cells homozygous for *Ext1* disruption can survive without difficulty, but fail normal patterns of differentiation [9]. Their lack of normal heparan sulfate cripples their differentiation capacity[10]. Most striking, however, is that this differentiation capacity can be restored by growing the cells within a gel environment that contains these glycosaminoglycan oligosaccharides (personal communication from Catherine Merry). Potential future clinical application includes the placement of glycosaminoglycan (GAG) bearing scaffolds into osteochondroma excision sites.

Molecular Biology

Although the precise enzymatic contribution of *EXT1* and *EXT2* to HS chain elongation remains mysterious, much is understood about the genes themselves. A new collaborative effort is underway called the Multiple Osteochondromas Database, or MODb., which records the 900 known mutation variants that are disease causing, including 550 unique mutation sites[11-12]. All such mutations that are well-characterized result in the loss of function of either *EXT1* or *EXT2*. The MODb collaboration aims to sort out some of the phenotypic variation, which may or may not associate with genotype.

Genotype-phenotype correlation studies have suggested that patients with *EXT1* mutations have more severe manifestations of disease than those with *EXT2* mutations[13], but further studies are underway with the newly available large databases of patients in Europe.

Exhaustive efforts to identify loss of heterozygosity, or second hit mutations in *EXT1* in the cartilaginous caps of osteochondromas continue[14-16]. Using a DHPLC/MLPA protocol and direct sequencing of all abnormal profiles, a second hit, or somatic disruption of the functional allele of *EXT1* or *EXT2*, is identified in only a minority of osteochondroma samples in some studies[17]. This raises the possibility that other epigenetic, post-translational, or other second hits are often the mechanism of *EXT* inactivation, or, more

critically, heparan sulfate polymerase inactivation, in the chondrocytes. One alternate second hit that has been suggested is the expression of a unique microRNA, or small, non-coding RNA that downregulates the expression of a panel of genes. Osteochondromas have been noted to have a unique profile of microRNA expression[18].

Cell Biology

A recent study has compared chondrocytes and mesenchymal stem cells, both retrieved from patients who have germ line heterozygous mutations in *EXT1*[19]. Compared to wild type cells, HS chain length and structure as well as *in vitro* chondrogenesis assays and expression signatures are indistinguishable in these heterozygous cells. A subpopulation of osteochondroma chondrocytes can be found to have a second hit, disrupting the inherited functional allele of *EXT1*. These cells exhibit all the aberrant function associated with pathogenesis.

Cilia have also been studied with regard to osteochondromas, due the disorganization of the cells in contrast to the highly ordered chondrocytes of the normal physis. A single cilium is prominent on normal chondrocytes, but decidedly missing on many osteochondroma chondrocytes[20].

Expression of HS with *Ext1* has also been shown to be critical to the normal interaction between murine fibroblasts and the extracellular matrix[21], enhancing this relationship between HS and cell-matrix and orientation interactions.

Non-Mammalian Models of Disease

Efforts to study the biology of *tout velou* (*ttv*), a fruit-fly, or *Drosophila melanogaster*, homologue to human *EXT1* generated some of the first understanding of this family of proteins. That trend has continued across the last decade. *Ttv* and *sister of tout velou* (*sotv*), the homologue of human *EXT2*, continue to lend insight into the biology of exostosins and osteochondromagenesis. *ttv* or *sotv* disruption in fruit-flies disturbs the signaling of the *Drosophila* homologues to the Hedgehog, Wnt, and BMP signaling pathways[22]. Further, the role of heparan sulfate proteoglycans (HSPGs) in the organization of embryogenesis is temporally controlled to the middle and later stages of embryogenesis. The absence of HSPGs allows bone morphogenic proteins (BMPs) to control the earlier stages[23].

An *ext2* null zebrafish has also been described[24]. Zebrafish are especially intriguing as a model organism for a null exostosin, as the maternal transcripts linger long enough to get even the homozygous mutants through gastrulation and early embryogenesis, permitting study of the effects on later stages of development in an otherwise germline null mutant. Zebrafish null for functional *ext2* lack the columnar organization of chondrocytes during skeletogenesis. Transplantation of these mutant chondrocytes into wildtype embryo cartilaginous elements rescues their phenotype when they are surrounded by wildtype chondrocytes, but not when they are transplanted to the surface of these elements (Figure 2). This offers one explanation for why we see no obvious intra-osseous phenotype in patients with MHE/MO, but an abundant bone surface phenotype. This work also makes an argument that the formation of osteochondromas, homologous to the disorientation of the chondrocytes in the zebrafish, requires loss of heterozygosity, or disruption of the second *EXT* allele.

Mouse Models of Multiple Osteochondromas

There has been some difficulty in modeling the formation of osteochondromas in mice. Mice that mimic the inherited genotype of heterozygous disruption of either *EXT1* or *EXT2*

in humans with heritable multiple osteochondromas have failed to mimic the human phenotype. A small minority of mice heterozygous for disruption of the homologous *Ext2* will form a solitary osteochondroma-like growth on a rib[25]. As with humans, mice homozygous for disruption of *Ext1* or *Ext2* do not survive to birth, failing to complete gastrulation in early embryogenesis[25-26].

The first genetic mouse model mimicking the human phenotype was achieved with a unique strategy to model the tissue genotype of somatic loss of heterozygosity, or the proposed method by which cells might lose the single functional copy of *Ext1*[27]. The mouse has *loxP* sites oriented in such a way that they recombine to generate inversion, rather than excision of the intervening critical fragment of *Ext1*. This inversion is reversible, such that a distribution of forward-functional and inverted-disrupted alleles of *Ext1* will result after exposure to *Cre*-recombinase. This generates an overall tissue disruption of half of the alleles of *Ext1*, but will generate some cells with homozygous disruption. Mice in which this disruption is induced in collagen II expressing chondrocytes form rampant osteochondromas (Figure 3). Indeed, all osteochondromas contained some cells with homozygous disruption of *Ext1*. The mouse further showed that the physal chondrocyte is the cell of origin, rather than the ossification groove of Ranvier as has been speculated previously.

Other mouse models developed since have recapitulated these findings using other conditional knock-out strategies[28-29]. Many, but not all osteochondromas also bear chondrocytes with functional *Ext1*, raising the possibility that sampling error alone might have created the previous challenge of data from some human specimens in which no loss of heterozygosity was identified in the osteochondroma chondrocytes. Most likely, critical reduction in heparan sulfate production is the necessary defect in the chondrocytes, whether this is achieved by loss of heterozygosity or by some other second hit (Figure 4).

Involvement of Non-Skeletal Tissues

The first mouse model of conditional inactivation of *Ext1* actually focused its attention on brain development and axonal guidance[30]. Alterations in the physiology of other tissues has also been studied to discern the effects of HS loss, including lymphocytes[31], the kidney[32], neural crest cells [33], the eye[34], and endothelium[35]. The biological importance of heparan sulfate is high in nearly all tissue types, but the mild truncation of HS chains, detectable in all tissues of patients heterozygous for mutations in *EXT1* or *EXT2*, does not have any clinically apparent phenotypes beyond the skeleton[36]. This is likely due to the mild character of the extraskeletal phenotypes and our lack of sensitive detection techniques to date.

Orthopaedic Surgical Interventions for Multiple Osteochondromas

Most of the surgeries for patients with MHE/MO are performed to correct growth deformities or remove symptomatic osteochondromas[37]. There is little to no hard evidence guiding any such decision-making, but many techniques have been used with good success. Periacetabular impingement is a challenge arising from the occasionally severe involvement of the femoral neck with osteochondromas (Figure 5). Valgus deformities of the knee and ankle are common, due to undergrowth of the fibula, which is frequently involved, tethering the tibia's lateral side (Figure 6).

The most common deformity in the upper extremity is caused by a length discrepancy between the radius and ulna. Like the fibula, the ulna tends to be especially affected. Radial bowing, radial tilting, and even radial head dislocation can result[38]. Releasing the ulna collateral carpal ligament at the wrist as prevention and radial head resection at skeletal maturity as treatment can both be used to manage impending or complete radial head

dislocation[39]. As for the ulnar wrist deviations generated from relative radial overgrowth, these are usually asymptomatic. A number of treatments, including both acute and guided-growth interventions have been successful in managing them (Figure 7).

Fortunately, malignant transformation of an osteochondroma into a surface chondrosarcoma is a very rare event, affecting less than two percent of patients with MHE/MO [1]. When it does occur, the chondrosarcomas that develop are typically low-grade and successfully eradicated with surgical resection alone (Figure 8). This rate is low enough and the tumors slow enough growing when they do arise, that routine screening of these patients for malignant transformation is controversial.

An argument for routine screening for spine involvement in MHE/MO has been made recently. The prevalence of spine involvement and encroachment on the spinal canal was found to be higher than expected[40]. Neurologically devastating consequences may be preventable by early detection of these spinal canal osteochondromas.

Related Diseases

Osteochondromas that form on the epiphyses of long bones are associated with a different disorder, called Trevor's disease, or dysplasia epiphysealis hemimelica[41]. It has only been studied in small case series alone, due to its low prevalence.

Recently, the vast majority of patients with fibrodysplasia ossificans progressiva, otherwise characterized by the development of disabling progressive heterotopic ossification, have been noted to have osteochondroma-like protuberances, especially on the proximal tibia[42]. This was a previously unrecognized manifestation of disease.

Another rare autosomal dominant disorder that is really just beginning to be well-characterized is called metachondromatosis. These patients develop periarticular metachondromas, like osteochondromas, but pointing toward the joint, and enchondromas. These patients have been confirmed not to have mutations in *EXT1* or *EXT2*. Mutations in *PTPN11* have recently been identified as the genetic etiology of the disorder[43].

Future Directions

The data published within the last year, including human genetic data and data from zebrafish and mouse models all point toward loss of heterozygosity as the pathogenetic mechanism by which osteochondromas are formed. The lack of identifiable second hits in *EXT* coding sequence in some osteochondromas is partly explicable by the noted presence of some wild-type chondrocytes within osteochondromas and the possibility that epigenetic second hits or other non-*EXT* second hits might also result in the critical reduction in heparan sulfate chain elongation (see again Figure 4).

This is a disease with a truly unique genetic pathogenesis, wherein loss of heterozygosity is required, but the tumor-like growths that develop are not actually clonal neoplasms. This certainly opens up the possibility that other diseases require similar tissue-mosaicism for loss of heterozygosity that has yet gone unrecognized.

Much work remains to sort out exactly which pathway disturbances are required and which might be targets of pharmacologic intervention to prevent formation or growth of osteochondromas. Also yet to be explained is the pathogenesis of the short bone (especially fibula and ulna) and short stature phenotype which is variably present. Is it due to growth potential steal phenomenon, or some dysplastic effect of generally shorter HS chains from the heterozygous mutation across the entire tissue? Also yet to be further studied are the

non-skeletal phenotypes related to *EXT* gene disorders, the careful population-based recognition in humans of phenotypes noticed in other species, and the identification of additional tissue phenotypes yet to be noticed at all.

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Figure 1.

The proteins expressed by the genes *EXT1* and *EXT2* form part of the heparan sulfate (HS) polymerase complex in the golgi apparatus, elongating HS chains on specific proteoglycans headed for the cell surface and extracellular matrix. Disruption of both copies of either *EXT1* or *EXT2* will critically impair the HS chain elongation process, and thus the function of the cell surface and extracellular matrix proteins that normally have HS residues. These disrupted proteins include a number of important signaling receptors and paracrine growth and differentiation factors.

Figure 2.

Cartilaginous elements lose their usually well-ordered stacks of chondrocytes in *ext2*-null zebrafish. If these cells are transplanted into the center of wildtype zebrafish cartilaginous elements, their lost polarity will be rescued and they will behave like wild-type chondrocytes. If transplanted instead to the surface of wildtype zebrafish cartilaginous elements, where they are not surrounded by the matrix produced by wildtype neighboring cells, they will maintain their lost-polarity phenotype, failing to grow in orderly fashion. This finding has implications with regard to the observation that osteochondromas form peripherally whereas the central growth plate remains apparently normal.

Figure 3.

Mice bearing a low-prevalence of homozygous disruption of *Ext1* in chondrocytes develop numerous osteochondromas near major skeletal growth centers. This CT scan from a 10week old mouse (A) faithfully recapitulates the human skeletal phenotype, including the definitional cortical and medullary continuity, displayed on this coronal reconstruction of a femur CT (B). Safranin-O histology from a small osteochondroma (C) in a 6 week-old mouse also demonstrates the cortical and medullary continuity and the loosely organized physis-like cap of the osteochondroma. This mouse model of osteochondromagenesis argues that loss of heterozygosity, or at least some additional genetic derangement is required for osteochondroma formation, rather than osteochondromas resulting from haploinsufficiency for *EXT1* or *EXT2*.

Figure 4.

This is a working model for osteochondromagenesis, assembling data from a number of the presentations at the meeting. Osteochondromagenesis is initiated in multiple osteochondroma patients or in the general population by genetic derangements that cripple a cell's capacity to elongate heparan sulfate (HS) chains. This derangement to a central physeal chondrocyte generates no phenotype, as it is rescued by the HS produced by its neighbors. When it happens peripherally, the cell loses polarity, eschews differentiation, and maintains a proliferative advantage, bringing other wildtype cells along as it grows into the cartilaginous cap of a budding osteochondroma.

Figure 5.

Involvement of the femoral neck can pose significant surgical challenges in patients with multiple osteochondromas (MO). They give new meaning to the term femoroacetabular impingement (A). The safe surgical hip dislocation described originally by Reinhold Ganz (B) is one method of approach for the circumferential debridement of osteochondromas that is at times required. This post-operative radiograph demonstrates the significant trimming that was safely performed (C). The single screw up the femoral neck was placed to help prevent pathologic fracture following the debridement. (Images are courtesy of Dror Paley and the Paley Advanced Institute for Limb Lengthening, West Palm Beach, Florida)

Figure 6.

This 9y.o. girl presented due to challenges related to valgus limb alignment. She was noted to have multiple hereditary exostoses with the common genu valgum secondary to relative undergrowth of the fibula, shown on this anteroposterior standing full-length radiograph of the lower extremities (A). This was corrected gradually over time, using guided growth from 8-plates applied across the medial physes on bilateral tibiae and femora (B).

Figure 7.

Due to the more severe effects on growth seen in the ulna of patients with multiple osteochondromas (MO), the relative radial overgrowth frequently causes ulnar deviation deformities at the wrist (A) and even radial head dislocations proximally (B). (Images courtesy of Scott Kozin and the Shriner's Hospital for Children, Philadelphia, Pennsylvania.)

Figure 8.

This 65y.o. male presented with a foot drop, progressive over months as what was once an osteochondroma of the proximal fibula and tibia transformed into a chondrosarcoma and began to grow. Plain radiographs before resection (A), a hematoxylin and eosin stained histopathology specimen (B), and radiographs after resection and knee reconstruction follow his course from diagnosis through definitive management.