Abstracts from Invited Speakers

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RARE SYNDROMES: WHAT THEY TEACH US ABOUT OSTEOARTHRITIS DISEASE MECHANISMS

J.A. Gallagher. Univ. of Liverpool, Liverpool, United Kingdom

William Harvey, the great English physician of the 17th century observed “Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows tracings of her working apart from the beaten paths; nor is there a better way of advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease”. Harvey’s words have indeed been prophetic; the biomedical literature contains numerous examples of how research on the extreme phenotypes of monogenic diseases has helped elucidate the molecular pathogenesis of more common disorders. Several therapies for common diseases, including the blockbuster drugs statins and bisphosphonates, were discovered in part through the study of rare syndromes.

Despite the examples from other fields on the wider benefits of rare disease research, the potential impact of studying less common cartilage syndromes on osteoarthritis (OA) has been relatively neglected. However, recent investigations from several laboratories have highlighted the more general lessons that can be learnt from research on diseases such as chondrodysplasias, familial chondrocalcinosis, Kashin-Beck Disease (KBD) and the osteoarthropathy of alkaptonuria (AKU).

While the rare mutations responsible for chondrodysplasias has identified genes such as GDF5, which plays a key role in skeletal development. Polymorphisms in this same gene provide one of the best characterised genetic associations with OA susceptibility. Mutation of the ANKH gene in chondrocalcinosis has highlighted the role that this gene plays in the physiological and pathological mineralisation of cartilage. The expression of ANKH, which codes for a pyrophosphate transporter is known to be dysregulated in OA. Research on KBD has identified aberrations in gene expression and cell signalling some of which are also observed in OA.

AKU is a single gene defect in tyrosine metabolism that leads to an early onset, aggressive joint degeneration. Although joint destruction in AKU is associated with the deposition of pigmented polymers in cartilage, termed ochronosis, there are several parallels with the pathophysiology of OA. Studies on tissue samples from patients with AKU, and from a mouse model of the disease, have revealed previously unrecognised microanatomical, cellular and biochemical changes in joints which have been subsequently also detected in human OA. These include early changes in the integrity of collagen fibrils, the role of calcified cartilage in the initiation of OA, thinning and cracking of the subchondral plate and aberrant non-Frostian bone remodelling with the formation of novel microanatomical structures described as trabecular excrescences.

All of these features are abundant and easily recognisable in the severe phenotype of AKU but require more careful observation in OA because they occur at a lower frequency.

In conclusion, there is overwhelming evidence that studying rare cartilage syndromes with extreme phenotypes can help elucidate the pathophysiological mechanisms involved in the initiation and progression of joint destruction. Further support for rare disease research “apart from the beaten paths” could make a significant contribution to the development of effective therapies for OA and the identification of new biomarkers.

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MICRO-RNA AND CHONDROCYTE FUNCTION

M. Sato. Tokai Univ. Sch. of Med., Isehara, Japan

MicroRNAs (miRNAs) are single-stranded non-coding RNAs of ~22 base pairs that regulate gene expression by repressing translation. In 1993, the first miRNA, lin-4, was discovered in nematodes, and subsequent studies have shown that miRNAs regulate ~30% of all human genes. miRNA is transcribed initially from miRNA genes into a long primary transcript (pri-miRNA), which is then cleaved by Drosha to produce precursor miRNA (pre-miRNA). The pre-miRNA is then transported to the cytoplasm using exportin-5, and there it is cleaved by Dicer to yield miRNA. The miRNA then combines with an argonaute protein to form RISC, which sequence-specifically recognizes and represses the translation of target RNAs. Abnormalities in cartilage development have been observed in Dicer gene dysfunction models, and miRNA is known to play a key role in cartilage differentiation. miRNA plays a key role in differentiation and growth in organs and tissues, and miRNAs expressed specifically in cartilage have been reported. To date, miR-21, miR-22, miR-27a, miR-140, miR-146, and so on have been reported as miRNAs that are associated with cartilage metabolism. Many studies have reported the use of a microarray analysis for isolating miRNAs that are expressed in a tissue-specific manner. For example, Miyaki et al. performed microarray analysis of mesenchymal stem cells and articular chondrocytes, and they observed a high expression of miR-140 in chondrocytes. They also observed that the expression of miR-140 increased during chondrogenesis. In addition, they reported that miR-140 expression was lower in the osteoarthritis (OA) group than in the normal group. Iliopoulos et al. performed microarray analysis using normal chondrocytes and chondrocytes isolated from OA. They reported an increased expression of miR-22 and a decreased expression of miR-140 in the OA group. They also reported that the expressions of IL-1beta and MMP13 were increased, whereas the expression of aggrecan was decreased in the group that showed increased miR-22 expression. On the other hand, using microarray analysis, we focused on three types of miRNAs, i.e., miR-199a-3p, miR-193b, and miR-320c, and their expressions were observed to vary with age. We harvested cartilage tissue from patients with polydactylysm, anterior cruciate ligament injury, and OA undergoing total knee arthroplasty, and we used microarrays to identify miRNAs whose expression is upregulated or downregulated with age. The results were assessed by real-time PCR and MTT assay in a mimic group, in which synthetic double-stranded RNA was transfected to upregulate expression, and in an inhibitor group, in which the miRNA was bound specifically to downregulate expression. The expression of two miRNAs (miR-199a-3p and miR-193b) was upregulated with age, and that of one miRNA (miR-320c) was downregulated with age. A real-time PCR assay showed that type 2 collagen, aggrecan, and SOX9 expression were upregulated in the miR-199a-3p mimic group but were downregulated in the inhibitor