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Editorial on Osteoarthritis Pathogenesis

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Editorial

Osteoarthritis is the most common joint ailment and a significant source of disability with significant socioeconomic consequences. In these instances, it is critical to comprehend the pathogenesis. Although past studies focused primarily on articular cartilage alterations, more recent research has underlined the role of the subchondral bone, synovium, menisci, ligaments, periarticular muscles, and nerves. Osteoarthritis is now recognised as a complex illness that affects the entire joint. Joint replacement for end-stage disease remains the only treatment, leading to an escalating healthcare crisis in our obese and ageing society. Osteoarthritis is a complex trait and the 86 reported genome-wide associated nerve centers explain only a small proportion of its heritability, which is estimated between 40 and 70%.

Osteoarthritis is characterized by articular cartilage damage and loss, together with structural abnormalities of subchondral bone and low-grade chronic joint inflammation. It is unknown which of these processes trigger disease or which represent secondary responses to joint destruction. It is also uncertain whether the pathogenesis of osteoarthritis reflects an abnormal response to injury involving defective stem cell recruitment and abnormal cell proliferation, differentiation, metabolism, apoptosis, and senescence.

An increase in anabolic and catabolic activity is seen in osteoarthritic cartilage. At first, compensatory mechanisms such as increased matrix molecule synthesis (collagen, proteoglycans, and hyaluronate) and chondrocyte proliferation in the deeper layers of the cartilage are able to keep the articular cartilage intact, but eventually, chondrocyte loss and changes in the extracellular matrix predominate, and osteoarthritic changes develop.

Chondrocytes in healthy articular cartilage are resistant to terminal differentiation, whereas they return to a developmental program following injury, in which they proliferate and undergo hypertrophic differentiation with accelerated cartilage mineralization. Osteoarthritis pathogenesis involves cross-talk between the synovium, articular cartilage, and subchondral bone, although the timing of bone remodeling relative to cartilage degradation remains uncertain. Nevertheless, increases in apoptotic and senescent chondrocytes are triggered by processes including endoplasmic reticulum stress. Senescent cells express a secretory phenotype that contributes to inflammation, vascular invasion, and cartilage breakdown via key pathways that stimulate matrix metalloproteases and aggrecan-specific proteinases.

Despite the profound clinical and socioeconomic impacts of osteoarthritis, our understanding of its genetic basis is in its infancy. We hypothesize that accelerating gene discovery in osteoarthritis will increase understanding of joint physiology and disease pathogenesis and facilitate identification of drug targets that prevent or delay joint destruction. Studies of extreme phenotypes in humans have strengthen identification of the molecular basis of single gene disorders and mechanisms of complex disease and resulted in new treatments. Analogous to our gene discovery studies in osteoporosis, we propose that a joint-specific extreme phenotype screen in mutant mice will accelerate functional gene discovery in osteoarthritis.

Mutant mice are generated at the Sanger Institute as part of the International Mouse Phenotyping Consortium (IMPC). Mice undergo broad phenotyping using the International Mouse Phenotyping Resource of Standardized Screen (IMPReSS) that is completed at 16 weeks of age when tissues are gathering for further analysis. In the Origins of Bone and Cartilage Disease (OBCD) Project we collaborate with IMPC and receive knee joints for analysis. Rapid-throughput phenotyping of the mouse knee requires quantitative imaging; this presents a complex and unsolved challenge that relates to anatomical size, three-dimensional complexity, image resolution, and the necessity to maintain joints in their native fully hydrated state.

Here we present the invention, optimization, validation, and application of a rapid-throughput multimodality imaging pipeline to phenotype the mouse knee. We examine 50 randomly selected mouse lines, identifying seven (14%) with markedly abnormal phenotypes. A systematic prioritization strategy identifies seven further lines, resulting in 14 genes (28%) with proof for a functional role in osteoarthritis pathogenesis. The four leading candidates are Pitx1, Bhlhe40, Sh3bp4, and Unk. We cross-examine the database of joint phenotypes from randomly selected mouse lines with 409 genes differentially expressed in human osteoarthritis cartilage. This results in an enriched yield of abnormal joint phenotypes in six (75%) of eight lines for which data are available, including Unk.

We then apply the pipeline to characterize the early features of age-related joint degeneration in 1-year old mice and illustrate its sensitivity to determine disease onset as well as surgically produce late-stage disease, paving the way for application to analysis of drug intervention studies. Finally, we phenotype previously generated CRISPR/Cas9 mutant mice with a Thr92Ala polymorphism in the Dio2 gene that is orthologous to the human variant associated with osteoarthritis susceptibility. The Ala92 allele confers protection against early-onset osteoarthritis, challenging current understanding with implications for public health.

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