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Translating genomics into mechanisms of disease: Osteoarthritis

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A B S T R A C T

Osteoarthritis (OA) is the most common age-related arthritic disorder and is characterized by aberrant extracellular matrix (ECM) content and surface disruptions that range from fibrillation, clefting and delamination, leading to articular surface erosion. Worldwide, over 20% of the population is affected with OA and 80% of these patients have limitations in movement, whereas 25% experience inhibition in major daily activities of life. OA is the most common disabling arthritic disease; nevertheless, no disease-modifying treatment is available except for the expensive total joint replacement surgery at end-stage disease. Lack of insight into the underlying pathophysiological mechanisms of OA has considerably contributed to the inability of the scientific community to develop disease-modifying drugs. To overcome this critical barrier, focus should be on translation of identified robust gene deviations towards the underlying biological mechanisms.

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Osteoarthritis disease background

Osteoarthritis (OA) is a prevalent, complex, disabling disease affecting the articular joints. Age, genetic factors and mechanical stress are some of the risk factors of OA. Currently, there is no adequate therapy to reverse or slow down the disease. Analgesia, physiotherapy and, in severe forms of the disease, joint replacement are the main treatment options. As a result, OA has a large and detrimental impact on the quality of life of elderly individuals and this increased morbidity contributes indirectly to an increased mortality [1].

Comprehensive genome-wide searches for genetic variants conferring risk for OA have resulted in robust genome-wide significant signals [2,3]. Functional follow-up studies, to show biological relevance, however, have only recently started to be implemented as a natural next step. Consequently, little progress has been made in clinical translation of these findings, let alone identification of novel evidence-based treatment options or disease-modifying OA drugs. This chapter provides a brief summary of the field of OA genomics and suggested common underlying pathways. Subsequently, an outline of proposed functional genomic research, including human joint tissues and three-dimensional (3D) in vitro cell and in vivo animal models, is provided and is exemplified by work on the susceptibility genedeiodinase iodothyronine type-2 (D2) gene (DIO2).

OA pathophysiology: role of dynamic regulation of gene expression

Articular cartilage is a connective tissue that covers the ends of long bones. It has a smooth, wear-resistant lubricated surface that allows bones to glide over one another with minimal friction, yet eligible to absorb impact forces. Chondrocytes in articular cartilage reside in a maturational arrested state without detectable proliferation and at a low metabolic activity [4]. Nonetheless, articular chondrocytes maintain cartilage tissue homeostasis throughout life and as such need to apply remodelling of extracellular matrix (ECM) upon stresses and micro-traumas [5]. To secure cartilage integrity and cope with these challenges, the chondrocyte is required to continuously and dynamically adjust expression of catabolic and anabolic genes, while maintaining its capacity to restore its maturational arrested steady-state phenotype [6]. This plasticity is likely maintained by virtue of epigenetic control mechanisms [7,8]. Multiple epigenetic layers exist, such as histone modifications, microRNAs and long non-coding RNAs. The most studied epigenetic mechanism is DNA methylation, the phenomenon in which the cytosine nucleotide that is located in cytosine–guanine (CpG) residue pairs gets methylated. The amount of CpG methylation facilitates dynamical adjustment of gene expression in a very context-specific manner and is directed by cellular requirements upon environmental exposures. Hence, epigenetic regulation of gene expression has been found to be an important mechanism by which the maturational arrested articular chondrocytes are able to appropriately adapt to a changing environment encountered due to, for example, biomechanical stresses yet allowing securing a steady-state tissue homeostasis [6,9]. Genetic variations [10] and stochastic events during ageing have, however, been shown to cause changes in epigenetic marks resulting in subtle differential (allelic) gene expression. Moreover, such changes have frequently been found to be associated with pathological conditions [11], including OA [12,13]. Given that chondrocytes in OA-affected cartilage have recapitulated a growth plate morphology and exhibit an articular cartilage-debilitating expression profile [14] similarly to that occurring at end-stage endochondral ossification [15], it was hypothesized that deviations in epigenetically controlled gene expression could be an underlying mechanism of OA pathophysiology [6,16].

Growth plate endochondral ossification is a developmental process of growth and bone formation. Herein, differentiation of chondrocytes results in the formation of a complex, longitudinally organized cartilage template which following elongation through chondrocyte proliferation will be replaced by bone. To allow gradual replacement of cartilage to bone matrix, growth plate chondrocytes become hypertrophic and commence terminal differentiation, followed by mineralization of the cartilage, apoptosis of the chondrocytes and vascular invasion [15]. In this process, local, intracellular active thyroid hormone (T3) is known to be essential in signalling terminal maturation of hypertrophic chondrocytes [17]. As such, endochondral ossification is essential during skeletal development; however, it is considered deleterious for mature articular cartilage and respective joint function (Fig. 1).