The latest global burden of diseases study reviewed 187 countries and 27 regions. Their report confirms what was already suspected by many clinicians and epidemiologists. Osteoarthritis (OA) is one of the commonest causes of disease burden worldwide, ranking as high as 11th as a contributor to global disability. This burden is increasing exponentially; the years lived with disability (YLD) for hip and knee OA has increased from 10.5 million in 1990 to 17.1 million in 2010. The study also confirms that the disease is ubiquitous and spread all over the surveyed geographical regions and was most commonly seen in females over the age of 50, though no age was exempt (1). It was a pleasure reading an article entitled “Increased DNA Methylation and Reduced Expression of Transcription Factors in Human Osteoarthritis Cartilage”, written by Oscar Alvarez-Garcia, which was published in Arthritis & Rheumatology in Aug. 2016 (2). The authors have shown that normal and OA knee articular cartilage can be distinguished by their DNA, methylation profiles. This raises an important issue of regulation of arthritic changes by epigenetic changes. Epigenetics is a complex process of chromatin and gene modulation through DNA methylation, histone deacetylation or microRNA, which might contribute to the inheritability of disease (3). OA is an age old disease of the old age characterized by degradation and calcification of articular cartilage, but the disease also affects the synovial tissue, ligaments as well as the bone; leading to chronic pain, limitation of joint movement and loss of physical function. The patient suffers from stiffness, joint pains, and joint swellings and may be incapacitated and unable to work.

Unfortunately, there is at present no specific molecule which can modify the disease natural history. Many molecules have been proposed and discarded as definitive treatment for OA and treatment is now mostly confined to analgesia, exercise and surgical joint modification including replacement. Much work has been carried out to elucidate the molecular processes which cause the disease in the hope of understanding mechanisms which would lead to the development of better methods of disease control. Studies have elucidated genetic, epigenetic, proteomic and other pathways which increase and modify the disease pathology (4). The pathogenesis of OA is multifactorial, with aging, obesity, and genetic susceptibility being the main risk factors (5). During OA development, articular chondrocytes (the only cell type in articular cartilage that is responsible for maintaining tissue homeostasis) undergo marked transcriptional and phenotypic changes that compromise their function and lead to cartilage degradation However, genome-wide association studies have shown only a small genetic variance component for OA, and recent evidence has pointed to epigenetic regulation as a key driver of the transcriptional alterations observed in OA chondrocytes (6).

Arthritis & Rheumatology published an editorial on “Is it time for epigenetics in osteoarthritis?” (7), and made a call to the research community to increase efforts concerning the role played by epigenetics in the development of OA. It was put forth that the characterization and analysis...
of cartilage DNA methylomes not only offers potential therapeutic targets for the treatment of OA, but also enables the design of a map of epigenetic marks that can help develop potential biomarkers for diagnosis, prognosis, drug response, chondrogenesis, or homeostasis from high-resolution screening technologies. In 2 years’ time several articles proved association between epigenetics and OA phenotypes. Different stimuli (environmental factors), such as joint injury, oxidative stress, and inflammatory cues, aging, diet, metabolic (Mt.b.) disorders, or both nuclear and mitochondrial genetics are prone to alter the DNA methylome in OA, leading to the development of different phenotypes of OA (8).

In recent years the epigenetic mechanisms associated with disease have garnered a lot of attention as evidence has been generated that epigenetic regulation is a key driver of transcriptional alterations observed in chondrocytes of OA patients (9). The term epigenetics was first introduced by Conrad Waddington in the early 1940s. The original definition was broad, but in recent times, epigenetics has been defined more narrowly as the “the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence.” (10). To put it very simply, epigenetics allows information in the long DNA sequence to be turned into expressed characteristics. These expressions can alter in each cell or group of cells thus changes can take place in response to environmental influences.

The epigenetic modifications can have many clinical implications. Environmental influences can cause changes which are relevant in disease causation and progression.

The two principal elements which cause these epigenetic modifications are methylation and histone modifications. Basically the process of methylation involves addition of a methyl group to a cytosine base and in mammals this takes place mainly at CpG dinucleotides (4). There is a growing body of evidence which suggests that DNA methylation plays an important part in the pathophysiology of OA (11). It has been suggested that this may occur in two ways: some individuals with poor epigenetic profiles may be susceptible to OA or that age related changes in the epigenome may lead to cartilage damage. There is some evidence for either point of view and it is quite possible that both mechanisms are responsible for the epigenetic changes in OA.

The development of comparatively cheap methylation arrays has now made it possible to develop genome wide DNA methylation profiles of cartilage and to compare diseased with normal cartilage. Studies tend to be focused on cartilage as it is the principal pathological feature of the disease. In addition, it is composed of a single cell type (12). Roach et al. (11) first hypothesized that abnormal gene expressions of clonal OA chondrocytes is associated with heritable epigenetic alterations in the DNA methylation pattern. Their study provided the first direct evidence of an association between the loss of DNA methylation and abnormal expression of MMP 3, MMP 9, MMP 13 and ADAMTS 4 by OA chondrocytes. Several studies subsequently confirmed these findings. However all these studies were unable to demonstrate causality as longitudinal studies of the same cartilage samples were understandably not done.

The advent of high-throughput arrays for the analysis of DNA methylation has significantly boosted the amount of epigenetic data that has emerged in the past few years. OA has taken part in this enhanced activity and is in fact quite well placed to do so, for two principal reasons: the central tissue involved in the disease process, cartilage, is readily accessible via joint replacement surgery; and the cartilage contains only a single cell type, the chondrocyte, thus limiting the scope for confounding heterogeneity that can be encountered when studying the epigenetics of a multicellular tissue in which cell-specific effects are likely.

Five methylation array analyses of cartilage DNA have been published in the recent years, focused on knee and/or hip OA. A number of interesting observations have emerged. For example, knee and hip cartilages are strikingly different, with DNA methylation differences at a number of genes, including homebox genes, which are key regulators of skeletogenesis. This is reminiscent of the joint-specific genetic effects touched on earlier, and suggests that cartilages from different parts of the skeleton are not only genetically but also epigenetically distinct. The DNA methylation studies have also revealed that genes that have previously been implicated in OA typically harbor CpG sites that are differentially methylated between OA and non-OA cartilage. This implies that the regulation of gene expression via DNA methylation is a major driver of the OA disease process (13).

Genome wide methylome studies have utilized more sophisticated arrays to analyze up to 485,000 sites. The results of these studies have been summarized by Reynard et al. (4).

DNA methylation contributes to the chronicity of OA and could be responsible for the limitation of current therapies. It may predict progression of the disease as well as response. Epigenetic treatments being used in oncology
may prove beneficial also in OA (14).

Ayugenomics, a recently evolving novel method combining the Ayurveda doctrine based constitution determination of study subjects with contemporary genome analysis tools, seem to hold promise for complex traits research efforts. A few groups in the country have already provided both preliminary and established evidence to show that personalized, predictive and protective health approach practiced in Ayurveda since 1500 BC can address some of the contemporary limitations and improve our understanding of biology of health and disease in molecular terms (15). Our recent study on DNA methylation changes in asthmatic individuals in response to Ayurvedic intervention using microarrays has shown encouraging results (16,17). Modalities from alternative and complementary medicine like Ayurveda are often pursued by many patients as well (18,19). Aqueous extracts of Withania somnifera root powder and fruit of Phyllanthus emblica have shown chondroprotective activities in an in vitro model of cartilage degradation with explant cultures of articular knee cartilage from OA patients (20,21). The possible mechanism of this unique activity of chondroprotection could be through epigenetic modifications or stem cell differentiation (22,23).

Mesenchymal stem cells (MSCs) have been proposed by many as an optimal regenerative cellular therapeutic for musculoskeletal regeneration, especially in the setting of degenerative pathology like OA (24,25). The translation of MSCs to clinical therapy for OA has been shown; however, signs of progress are evident and ongoing trials may show efficacy to indicate these products can serve as the disease-modifying therapy necessary to stem the tide of OA. MSCs have been used in several clinical studies, clinical trials and have been shown to have improved symptoms and developed articular cartilage. Two of the most recent studies are summarized here. A single arm open label Spanish study from Barcelona (26) recruited 15 patients with grade II or III OA and injected round 40 million autologous MSCs into the joint. The patients were followed up for 6 months and the efficacy of the procedure was measured by the visual analogue scale for pain, algofunctional Health Assessment Questionnaire, quality of life (QoL) SF-36 questionnaire, Lequesne functional index and WOMAC score. The cartilage integrity was assessed by magnetic resonance imaging (MRI) and quantitative T2-mapping at 0, 6 and 12 months. There were mild side effects, but improvements were noted in all the criteria for efficacy and cartilage growth was also noted by MRI. Another study (27) also from Spain used a multicenter randomized design to compare two doses of cultured autologous MSCs with hyaluronic acid. In this study, similar results were obtained. MRI studies also showed cartilage growth. There are many similar studies on these lines (28). However the clinical improvements are difficult to explain. Earlier hypotheses of cartilage regeneration by the MSCs are not now generally accepted. However it remains to be seen whether autologous/allogeneic MSC therapy works via reversing the epigenetic changes occurring during progression of OA. Since the epigenetic changes are reversible it would be interesting to see whether interventional therapies for degenerative diseases like OA modify the DNA methylation pattern and facilitate cartilage regeneration.

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Footnote
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References


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