EULAR study group on OA

Osteoarthritis Research Agenda

From clinical problems to pathophysiological research goals

The purpose of this document is to translate clinical problems in OA into pathophysiological research goals to facilitate the translation from Bed to Bench and vice versa.

Osteoarthritis is a huge and still increasing problem

Osteoarthritis (OA) is the most prevalent joint disease and accounts for more disability among the elderly than any other disease. It is estimated that OA affects about 40 million people in Europe[1]. Osteoarthritis can affect each and every joint but is most common in the knee, hip, spine and hand. Clinically it is characterized by joint pain, limitation of movement, tenderness, stiffness, crepitus and various degrees of inflammation. Osteoarthritis is considered a whole organ disease and structurally cartilage fibrillation, fissures, full thickness loss of articular cartilage, osteophyte formation, changes in the subchondral bone plate and fibrotic and inflamed synovium/capsule are seen.
To provide exact numbers of the incidence and prevalence is a difficult task. A major cause of this is the fact that radiographic changes are not always associated with joint pain and vice versa. Moreover, OA is a disease with, in general, a slow progressive nature. Studies are difficult to compare due to difference in study population and disease criteria. Osteoarthritis is relatively infrequent in people under the age of 40 years but increases definitely with age. Under the age of 45 women are less affected than males which reverses above the age of 45. Europe has a strongly ageing population and an obesity epidemic, old age and obesity being both major risk factors for OA. Since no therapeutic options, other than joint replacement are available, the burden of OA will continue to rise in the coming decades.

Absence of effective pharmacological treatment

Analgesics, such as paracetamol, opiates, non-steroidal anti-inflammatory drugs (NSAIDs), intraarticular hyaluronates are prescribed for treating pain but their effect is small (mean effect-size from 0.15 to 0.30). Osteoarthritic joints that show signs of inflammation are often treated with intraarticular corticosteroids. Another very important opportunity in OA management is change in life-style, mainly by increasing physical activity and improving physical condition and weight loss. Trials are ongoing with newer treatments of joint pain that are promising but sometimes with limitations due to drawbacks on structural features of anti-NGF treatment [2].

Treatment of structural deterioration of OA joints is still a big challenge. Nutraceuticals and viscosupplementation are prescribed for that aim although there is not enough evidence to claim this property. Studies with strontium ranelate show effects on joint space width, but the clinical relevance

of this small difference and the potential cardiovascular side effects have justified to halt its development. Ultimately, joint replacement is the option for patients with severe symptoms and end-stage OA. Joint replacement is a rapidly increasing procedure and over 90% of joints are replaced due to OA. However, this is a costly procedure and is, especially in relatively young people, not a permanent solution. Moreover, around 20% of the patients remain being painful even when the procedure has been successfully performed. Thus, the unmet needs in these patients are high and the development of OA treatments that can both prevent or treat structural break down and improve symptoms is increasingly needed. Personalized treatment, that a target patient-specific mode of action, requires biomarkers that stratify patients based on OA subtype specific pathophysiological processes.

Patient and researcher perspective

As is adequately exemplified by the paper of Kraus et al. the perspective on OA from a researcher's view point is quite different from the perspective of an OA patient[3]. While the main focus of the researcher is on genes, proteins and cells, signaling and metabolic pathways and structural aspects, the focus of the patient is on pain, functional limitations, aesthetic damage due to bony proliferations and loss of daily and social activities. A researcher views OA as a "*disease"* based on its abnormalities in structure and function originating from biological or (bio)chemical evidence while a patient considers OA as an illness, *"the human response to disease*"[4].

Originating from basic pathophysiological research questions, researchers have made major steps in understanding OA. We have come from the opinion on OA as a simple wear and tear process of articular cartilage to a concept of OA as a organ disease being in interaction with the human body as a whole. Our understanding is increasing enormously and only some general insight can be mentioned here. Genetic studies have shown that specific nuclear and mitochondrial gene variants (Smad3, Dio2, GDF5, etc) are associated with OA prevalence and or severity[5, 6]. The role of ageing and cell senescence has been implicated in OA[7]. Furthermore, it has been shown that changes in chondrocyte behavior like increased production of proteolytic enzymes, and even most likely changes in chondrocyte differentiation, play a crucial role in degradation of the articular cartilage matrix[8, 9]. These changes in chondrocyte behaviour are governed by changes in activated signaling pathways and changed responses of aged and senescent chondrocytes to these stimuli[10, 11]. Changes in the subchondral bone can predict subsequent symptoms or structural progression and recently it has been shown that not only local joint inflammation but also low grade systemic inflammation contribute to the OA disease process[12-14].

To gain a more robust understanding of processes that occur in OA, it is important to take into account interactions between gene expression, epigenetic regulation and environment in clinically well-defined patients.

OA phenotypes

Osteoarthritis has been historically classified based on joint location but not on the underlying pathophysiological process[15]. More and more it becomes clear that OA, even in a specific joint, can be classified due to specific features that presumably are a result of specific underlying disease processes[16]. End stage OA in a particular joint in different patients can be the final outcome of a variety of pathophysiogical processes that differ, or have differed, between these patients. Classification, not based on location, but on the underlying disease process will be a valuable instrument not only to further elucidate OA pathophysiology but also to optimize clinical trials.

Not only classification in OA phenotypes can be a major improvement, also early detection of OA is of crucial importance. As a result of its subclinical disease process in its early stage the initial changes in an OA affected joint remain under the radar. As a consequence, intervention is nowadays only started when severe, and even maybe irreversible, structural damage has occurred. To improve disease modifying intervention methodology has to be developed that can detect early OA changes and track the result of intervention.

OARSI definition of OA

Osteoarthritis is a heterogeneous disease and in this document we will use the draft definition of OARSI[3] as a working definition. We are fully aware that this definition will be modified according to further elucidation of the OA process(es) and disease phenotypes.

"Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness."[3]

Translation of clinical problems into pathophysiological research goals

The paper Conaghan et al. identifies 4 research priority areas[1]. In this paper we use these categories to classify our pathophysiological research goals. Below is a list of research goals based on clinical problems.

Major Pathophysiological research goals

Epidemiology (Genetic epidemiology)
To identify and elucidate the role of genetic variants in OA phenotypes
To identify and elucidate the role of epigenetics in OA phenotypes
To identify and elucidate the role of mitochondrial genetic variants in OA phenotypes
Imaging and Biomarkers
Identify markers for early OA
Identify markers for OA phenotypes
Identify markers for disease activity
Identify markers for disease progression
Identify predictive markers of therapeutic response
Identify markers to evaluate the therapeutic response
Pathogenesis
To understand tissue communication in OA (between cartilage, subchondral bone, synovium, vessels, adipose tissue)
To understand non-cartilage pathology in OA
To understand the role of chondrocyte differentiation in OA
To understand the role of joint trauma and repair in OA
To understand the mechanism of mechanical joint injury and the translation to inflammation and repair
To understand the relationship between synovitis and radiographic progression
To understand the earliest stages of OA
To understand the difference between OA phenotypes
To understand the origins of pain
To understand the relationship between pain and structure
To understand the relationship between synovitis and pain
To understand the relationship between ageing and OA
To understand the relationship between gender and OA
To understand the role of systemic factors in OA
To define the mechanisms by which co-morbidities influence the OA process (fat and glucose metabolism)
Therapy
To identify and validate targets for therapy (pain and structure)

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