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Review

Reactive oxygen species and NADPH oxidase 4 involvement in osteoarthritis

S. Drevet[a,*], G. Gavazzi[b], L. Grange[c], C. Dupuy[d], B. Lardy[e]

[a] Grenoble Alpes University Hospital, Orthogeriatric Unit, Geriatric Department, Grenoble Alpes University, GREPI UGA-EFS EA7408, Boulevard de la Chantourne, 38043 Grenoble Cedex 1, France
[b] Grenoble Alpes University Hospital, Acute Geriatric Medicine Unit, Geriatric Department, Grenoble Alpes University, GREPI UGA-EFS EA7408, Boulevard de la Chantourne, 38043 Grenoble Cedex 1, France
[c] Grenoble Alpes University Hospital, Rheumatology Department, Hopital Sud, GREPI UGA-EFS EA7408, 19 avenue de Kimberley, 38130 Echirolles, France
[d] Institut Gustave Roussy, UMR 8200 CNRS "Stabilité génétique et Oncogenèse", 114 rue Edouard Vaillant, 94805 Villejuif Cedex, France
[e] Grenoble Alpes University Hospital, Biology Department, Grenoble Alpes University, GREPI UGA-EFS EA7408, Boulevard de la Chantourne, 38043 Grenoble Cedex 1, France

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ABSTRACT

Osteoarthritis (OA) is a degenerative chronic disease affecting > 300,000 million people around the world as of 2016. Symptomatic measures exist, but there are hardly any curative treatments available. Disruption of the cartilage homeostasis in favor of catabolism leads to cartilage destruction. ROS-macromolecular-induced damage is significantly greater in OA cartilage and OA is described as low-grade chronic systemic inflammation. This review aimed to assess the critical role of cartilage ageing and oxidative stress in the OA process, focusing in particular on NADPH oxidase and especially Nox4 involvement. With age, hypertrophic senescent cells with an altered redox cell profile accumulated. Chondrocytes are more sensitive to oxidant-mediators and the serum level of pro-inflammatory mediators increases. Age-related advanced glycation end products impact on extra cellular matrix (ECM) properties leading to the apoptosis of chondrocytes. A focus on NADPH oxidase-mediated-ROS signaling highlighted the very specific Nox4 isoform, which plays a role on the final common pathway targeting chondrocyte cells. IL-1β-mediated Nox4 stimulation induced an increase in the levels released by the chondrocyte of MMP-1 and MMP-13 proteins, which are involved in ECM degradation. In comparison with the other Nox isoforms, Nox4 remains unusual, since it is constitutively active, does not depend on cytosolic activator proteins and seems to generate H_2O_2 thanks to the specific conformation of the Nox4 E-loop. Nox4-induced ROS production appears an essential actor in the OA process and it could be relevant to focus on this target in the aim of discovering and developing new therapeutic strategies.

1. Introduction

Osteoarthritis (OA) is a chronic degenerative disease affecting > 300,000 million people around the world in 2016 ("Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries 1990–2016," 2017). Prevalence increases with age, and OA is one of the most co-occurring diseases among patients aged 55 years and older (van Oostrom et al., 2014), with a positive association between multimorbidity and functional limitations (Jindai et al., 2016). This multi-dimensional health problem has a major impact on patients' quality of life and conditions of ageing, and incurs significant direct and indirect costs for society (Le

Abbreviations: ADAMT, aggrecanase disintegrin and metalloproteinase with thrombospondin Motifs; AGE, advanced glycation end products; Akt, protein kinase B; AP, activator protein; CRP, C-reactive protein; ECM, extra cellular matrix; DAMP, damaged associated molecular pattern; ERK, extracellular regulated kinase; FAD, flavin adenine dinucleotide; GKT, Genkyotex; GPX, glutathione peroxidase; HIF, hypoxia inducible factor; IFN, interferon; IGF-BP, insulin growth factor-binding protein; Ihh, Indian hedgehog; IL, interleukin; JNK, c-jun-N-terminal Kinase; MAP, mitogen activated protein; MMP, Matrix metalloprotease; MIA, monosodium iodoacetate; NADPH, nicotinamide adenine dinucleotide phosphate; Nox, NADPH oxidase; NF-kb, nuclear factor kappa-light-transcriptor factor; Nos, nitric oxidase synthase; OA, osteoarthritis; OS, oxidative stress; PDI, protein disulfide isomerase; PKC, protein kinase C; PKR, double-stranded RNA-dependent protein kinase; PMA, phorbol myristate acetate; Poldip, polymerase delta-interacting protein; Rac, ras-related C3 botulinum toxin substrate; ROS, reactive oxygen species; RUNX-2, Runt-related transcription factor 2; SOD, superoxide dismutase; TIMP, tissue inhibitor of MMP; Tks, tyrosine kinase substrate; TNF, tumor necrosis factor; TLR, toll-like receptor; XOD, xanthine oxygen oxidoreductase

* Corresponding author.
E-mail addresses: SDrevet@chu-grenoble.fr (S. Drevet), GGavazzi@chu-grenoble.fr (G. Gavazzi), LGrange@chu-grenoble.fr (L. Grange), corinne.dupuy@gustaveroussy.fr (C. Dupuy), BLardy@chu-grenoble.fr (B. Lardy).

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Pen et al., 2005). Several risk factors seem to be involved in developing OA (Buckwalter et al., 2004) (Lotz and Loeser, 2012) (McCulloch et al., 2017). Preventive and symptomatic measures exist, but there are hardly any curative treatments available, and new therapeutic targets are much needed (Morel et al., 2015). OA is characterized by a disruption of cartilage homeostasis in favor of catabolism, leading to cartilage destruction. This multifactorial disease not only affects the cartilage structure, but all of the joint tissues, including intra- and periarticular tissue, generating systematic disease. At least three main OA phenotypes are currently identified: age-related OA, post-traumatic OA and metabolic OA (Bijlsma et al., 2011), while Sellam et al. have suggested genetic and pain OA in the classification of OA phenotypes (Sellam and Berenbaum, 2013). Whatever the underlying cause, OA is one form of low-grade chronic systemic inflammation (Mobasheri et al., 2015) (Greene and Loeser, 2015) (Goldring and Otero, 2011). Molecular mechanisms are not well established but literature published over the last decades describes links between ageing, OA and inflammation (van der Kraan et al., 2017) (Rahmati et al., 2017). Pro-inflammatory cytokines are the key drivers of inflammation, and reactive oxygen species (ROS) are involved in the process. Mitochondria and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (Nox) activity are the two main sources of ROS production. This ROS production is needed to ensure the maintenance of cartilage homeostasis, but under some conditions, ROS can exceed anti-oxidant defenses, causing oxidative stress (Lepetsos and Papavassiliou, 2016). After establishing the pathophysiology and the critical role of cartilage ageing, this review will focus on Nox-mediated-ROS signaling and assess how ROS are widely involved in each level of the OA process. We will highlight in particular one very specific Nox family enzyme, the Nox 4 isoform, which plays a role on the final common pathway targeting chondrocyte cells.

2. Pathophysiology of osteoarthritis

OA may be classified as either primary, when it occurs on abnormal cartilage with normal loading, or secondary, when the disease results from an abnormal loading on normal cartilage. A set of OA risk factors is identified and may additionally participate in the degenerative process. Systemic factors include epigenetic and genetic factors, age, sex, diabetes, obesity, and metabolic syndrome. On the other hand, OA may result from mechanical stress (Buckwalter et al., 2004) (Lotz and Loeser, 2012) (McCulloch et al., 2017) (Hellevik et al., 2018). Since the local articular description, the list of impacted target tissues is increasingly longer. The first element to be described was the intra-articular part, with cartilage breaking down, synovial membrane inflammation and hypertrophy, subchondral bone remodeling, osteophytes and sclerosis. In a second phase, whole peri-articular tissues were outlined: muscle atrophy, unbalanced fat metabolism, capsule, ligament and tendon dysfunction. It was only later that the concept of systemic pathophysiology was highlighted, while entertaining the idea that the main actor in the final common path is the chondrocyte. Modifications of inter-cellular and inter-tissular interactions allow phenotype – function alterations in the chondrocyte.

The disruption of cartilage homeostasis towards catabolism leads to fibrillations and fissures of the articular cartilage surface (Fig. 1. There are both quantitative and qualitative modifications of the structure of the cartilaginous tissue (Fig. 2. OA induces a loss of extracellular matrix, chondrocyte apoptosis and overexpression of type X and type I collagen instead of type II collagen. The timeline of the process can be divided into three phases. The first stage is characterized by cartilage swelling due to the failure of attempted repair. Both catabolic and anabolic function are increased with cell proliferation, an increase in matrix proteins, proteinases, growth factors and cytokines (Goldring and Goldring, 2007). The biomechanical properties of cartilage are affected by the poor quality of synthesis products. Proteoglycan overproduction leads to cartilage hyper-hydration with tissue softening, and the scarcity of collagen fiber alters the cartilage's resistance, leading to micro-cracks. On the other hand, anabolic dysfunction leads to osteophyte production.

The second stage is characterized by superficial cracks arising from up-regulation of cell catabolism, and extra cellular matrix (ECM) proteolysis (Yudoh et al., 2005) (Gowen et al., 1984). In response to abnormal chondrocyte activation, cells are able to increase the synthesis of Matrix metalloproteinases (MMPs). MMPs are soluble key proteases (MMP-1 (collagenase 1), MMP-3 (stromelysine 1), MMP-8 (collagenase 2), MMP-2; -9 (gelatinase A and B) and -13 (collagenase 3)) leading to degradation of the ECM. MMP-13 has also been identified as a marker of differentiation in hypertrophic chondrocytes, and it plays a critical role in OA physiopathology (Ma et al., 2018). The proteolysis control system mediated by tissue inhibitor of MMPs (TIMPs) is not sufficient to maintain cartilage homeostasis. The dysregulation of the MMPs/TIMPs ratio in the synovial fluid is involved in the catabolic pathway (Xu et al., 2008). MMPs not only degrade ECM compounds but also cleave and activate catabolic cytokine precursors (IL-1, TNF-α) and anabolic proteins like IGF-BP (insulin growth factor- binding protein), with a crucial modification to the chondrocyte's microenvironment in a self-sustained process. IL-1β is usually not present in the healthy joint but in OA conditions it is one of the key pro-inflammatory cytokines. Osteoarthritic patients have an elevated level of IL-1β in the whole joint: synovial fluid, synovial membrane, cartilage and subchondral bone. Its local synthesis depends on chondrocytes, osteoblasts, synoviocytes and mononuclear cells after infiltration in the joint (Wojdasiewicz et al., 2014). IL-1β acts as a paracrine and autocrine factor inducing new IL-1β synthesis by chondrocytes, which further supports the pro-inflammatory conditions (Rousset et al., 2015). The cell cycle is disturbed, leading to proliferation, hypertrophic differentiation with a maturity-arrested differentiation state, chondrocyte senescence, and cell apoptosis (Charlier et al., 2016) (Dozin et al., 2002).

In the final stage, chondrolysis reaches the deep layers of cartilage until the subchondral zone and chondrocytes become hypertrophic or apoptotic. Collagen X, MMP-13, Runt-related transcription factor 2 (RUNX-2), and Indian hedgehog (Ihh) are the markers expressed during this terminal differentiation state (Mariani et al., 2014).

The up-regulation of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-18, CRP) and mechanical stress seem to be the first steps in OA pathogenesis (Fig. 3). Ligand/receptor interaction and integrin cell surface activation (Iannone and Lapadula, 2003) constitute the interface between chemical or mechanical stimuli and biochemical intracellular pathways. Rousset et al. demonstrated in vitro that IL-1β stimulation led to Nox4 activity enhancement with an increase in ROS production (Rousset et al., 2015). TNF-α was able to mediate MMP-2 and MMP-9 up-regulation (Gilbert et al., 2004), increase Nox activity and ROS production with accumulated oxidative stress responsible for IL-8 secretion (Ma et al., 2018). The three subfamilies of the mitogen activated protein (MAP) kinase pathway are involved in cell growth, proliferation and differentiation via extracellular regulated kinase (ERK), in cell survival via JNK (c-jun-N-terminal Kinase) and in cytokine production via p38 MAP kinase. All are implicated in matrix degradation by inducing MMP-13 up-regulation. The nuclear translocation of NF-kB up-regulates MMP-3, MMP-13, and collagen X leading to ECM degradation and hypertrophic state differentiation of the chondrocyte, until cell apoptosis (Mariani et al., 2014). NF-kB is also described as a key regulator for the hypoxic maintenance actors. MAPK, NF-kB and others (activator protein (AP-1), Hypoxia Inducible Factor (HIF-1α), Wnt-β catenine) are known as redox-sensitive targets (Pantano et al., 2006). The Nox enzymes mediate a large part of redox signaling and contribute to regulating interactions between decisive players.

OA risk factors, target tissues and the large number of elements represent a complex interactive network. The chondrocyte is the targeted cell of this multi-dimensional disease and MMPs play a crucial role in degrading the ECM. OA is associated with inflammation, and