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Osteoarthritis year 2011 in review: biology

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SUMMARY

This review is focused on advances in understanding the biology of joint homeostasis and osteoarthritis (OA) pathogenesis mechanisms that have led to proof of concept studies on new therapeutic approaches. The three selected topics include angiogenesis in joint tissues, biomechanics and joint lubrication and mitochondrial dysfunction. This new information represents progress in the integration of mechanisms that control multiple aspects of OA pathophysiology.

Keywords

Angiogenesis; Autophagy; Lubricin; Mitochondria

Introduction

The OA disease process affects all joint tissues, leading to joint dysfunction and pain and systemic and organismal changes that reduce quality of life, initiate or aggravate co-morbidities and reduce life expectancy. Progress in understanding the biology of joint homeostasis and disease mechanisms is essential for the development of new approaches to prevent or treat OA. To cover the general topic ‘biology’ assigned to this review, areas of biology that are most relevant to OA were considered. These include developmental biology of joints and joint tissues, stem cell biology, cell and molecular biology of adult joint tissue homeostasis, mechanobiology, extracellular matrix biology, systems biology and the biology of aging. These areas of biology provide a knowledge base for research on the pathobiology of OA. OA biology can also be viewed on the basis of scale, ranging from molecular to cellular, tissue, organ and organism level processes that determine risk for onset and progression of the disease or are affected by the disease process.

As an in depth review of all areas of biology is not possible within this manuscript, three fields, angiogenesis, joint lubrication and mitochondrial homeostasis were selected for

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detailed review to illustrate how progress in biology has led to identification and preclinical validation of new targets for the treatment of OA.

Angiogenesis

The formation of new blood vessels has previously been recognized as essential for the development of synovial hyperplasia[1] in arthritic joints where the synovial membrane becomes thickened, from increased proliferation of synovial fibroblasts, which also deposit new extracellular matrix. The formation of new blood vessels that supply oxygen and nutrients is not only necessary for the development of the hyperplastic synovium but also leads to tissue infiltration with blood-derived inflammatory cells and mediators. Synovial angiogenesis has been studied extensively in rheumatoid arthritis (RA). Many studies on angiogenesis compared RA, OA and normal synovium and the general conclusion is that angiogenesis correlates with the extent of synovial hyperplasia, which is most severe in RA, but also present in OA-affected joints[2]. The prominent role of synovial hyperplasia in RA has led to studies targeting mediators of angiogenesis such as vascular endothelial growth factor (VEGF) and this has been successful in RA animal models[3].

The importance of angiogenesis in OA is further supported by recent observations that new blood vessels are not only formed in synovium but also in other tissues. Normal articular cartilage is avascular, and this has been related to the presence of angiogenesis inhibitors, such as thrombospondin, chondromodulin[4], and collagen XVIII-derived endostatin[5]. OA articular cartilage is invaded at the osteochondral junction by blood vessels from the subchondral bone, which leads to increased blood vessel density in the non-calcified cartilage[6]. The osteochondral angiogenesis is also associated with subchondral bone marrow replacement by fibrovascular tissue expressing VEGF, and with increased nerve growth factor (NGF) expression within vascular channels that contain sensory nerve fibers[6]. In OA joints, increased angiogenesis is also observed in menisci along the fibrocartilage junction with increased penetration into the inner region[7]. These new blood vessels are also surrounded by sensory nerve fibers. The anterior cruciate ligaments from OA-affected human joints show increased numbers of blood vessels in the synovial sheath and within the ligament substance, where the new blood vessels are surrounded by cell aggregates[8]. Blood vessels and nerves also penetrate newly formed cartilage in osteophytes at the joint margins[9].

OA joints contain increased levels of VEGF in articular cartilage and synovial fluid and several cytokines that stimulate VEGF production are present[10, 11]. The increased VEGF production in OA has also been linked to the shift in hypoxia inducible factors and the abnormal hypertrophic differentiation of OA chondrocytes[12]. Growth plate chondrocyte hypertrophy physiologically generates angiogenic factors to initiate vascular invasion of the hypertrophic zone[13].

This new information that neovascularization is a feature of several tissues in OA joints and the association of angiogenesis with increased new sensory nerve fiber formation supports the hypothesis that these processes contribute to both structural change and pain in OA[14]. To test this hypothesis in the rat meniscectomy model of OA, PPI-2458, a specific inhibitor of endothelial cell proliferation was administered. PPI-2458 reduced synovial and osteochondral angiogenesis, synovial inflammation, cartilage damage and osteophyte formation. Importantly, this treatment also reduced pain behavior[14]. This study was the first to establish simultaneous benefit of an angiogenesis inhibitor on structure and pain modification in an OA model.

Several previous studies support angiogenesis inhibition as a promising approach for OA. Adenovirus-mediated thrombospondin-1 gene transfer in an OA model in rats significantly

reduced microvessel density, inflammation, and suppressed OA progression[15]. The limitation of this study was that thrombospondin-1 has activities in addition to inhibition of angiogenesis that may contribute to the observed effects. In a cartilage repair model, the use of stem cells that overexpressed the VEGF antagonist sFlt-1 reduced angiogenesis and improved new cartilage tissue formation without osteophyte development[16]. Angiogenesis inhibition through chondromodulin prevented chondrocyte hypertrophy and stabilized the articular chondrocyte phenotype[17].

Collectively, these new observations motivate further studies on the use of more specific and potent angiogenesis inhibitors in OA to better understand interactions between angiogenesis, cartilage and bone remodeling and pain mechanisms. The availability of antiangiogenic drugs that are approved for certain types of cancer and eye diseases[18] facilitates clinical evaluation of this approach in OA.

The Mitochondria-Autophagy Connection

Much of the progress in understanding OA pathogenesis is related to mechanisms that are activated in established disease. More recent efforts are directed at defining early changes that predispose or lead to the onset of OA[19]. As the majority patients develop OA as a function of increasing age, it is essential to understand aging-related changes in cell function. The phenomenon of cell aging includes reduced cell proliferation and extracellular matrix synthesis and increased production of reactive oxygen species, inflammatory mediators and extracellular matrix degrading enzymes[20]. This altered pattern of gene and mediator expression has been designated as the senescence-associated phenotype[21].

Two major mechanisms, telomere and mitochondrial dysfunction contribute to cellular aging and senescence. Shortening of telomeres in highly proliferative organs activates p53-dependent growth arrest, senescence and apoptosis[22]. Tissues with lower cell proliferation rates such as muscle or cartilage are equally affected by the aging process, largely through reactive oxygen species (ROS) induced genotoxic stress. A new model, which links telomere shortening, p53 activation and mitochondrial dysfunction was proposed in 2011. According to this model, the telomere-p53 axis suppresses PGC-1α or PGC-1β, which are the master regulators of mitochondrial biogenesis and metabolism and this leads to deficient ATP production and increased ROS generation, contributing to abnormal gene expression and cell death[23, 24]. Mitochondria also have an important role in pro-inflammatory signaling, as they initiate formation of inflammasomes and activation of other inflammatory pathways[25].

A series of prior studies demonstrated mitochondrial dysfunction in various OA models and in human OA. In addition, mitochondrial DNA mutations are increased in OA chondrocytes[26]. During the past year, new insight was provided on genetic risk factors and mechanisms of mitochondrial dysfunction, and defects in the protection against and removal of abnormal mitochondria in OA.

Rego-Perez et. al. had previously reported that mitochondrial DNA haplogroups contribute to OA risk as disease prevalence in haplogroup H was significantly higher compared to haplogroup J. In their recent study, they showed that serum levels of MMP-13 were significantly higher in patients with OA, and carriers of haplogroup H[27]. These observations provide further support for a genetic risk factor that can manifest as mitochondrial dysfunction.

Scott et. al. analyzed expression of all three forms of superoxide dismutase, enzymes that protect against ROS-mediated cell damage. The expression of these 3 enzymes was downregulated in cartilage from human OA joints and guinea pigs with spontaneous OA. In

particular, the mitochondrial SOD2 was reduced and the decline in SOD2 preceded OA-like lesions in the animal model[28].

The principal mechanism for removal of dysfunctional mitochondria is autophagy, or specifically, mitophagy[29]. Autophagy is mediated by formation of double-membrane vesicles, termed autophagosomes that sequester organelles, proteins, or portions of the cytoplasm. Autophagosomes then fuse with lysosomes, the sequestered contents are degraded by lysosomal enzymes and recycled as a source of energy[30].

Autophagy is compromised in OA cartilage and this is in part related to reduced expression of autophagy regulators[31]. New observations by Terkeltaub et. al. indicate that AMPK, which is a key regulator of autophagy activation under conditions of low energy or other stress conditions is reduced in OA cartilage and in chondrocytes following treatment with IL-1β or TNFα. AMPK activators attenuate dephosphorylation of AMPKα and procatabolic responses in chondrocytes induced by these cytokines[32].

The scenario suggested by these new observations is that mitochondrial DNA haplotype H, acquired mitochondrial DNA mutations and the telomere-p53-PGC1 pathway contribute to mitochondrial dysfunction, which is further aggravated by deficient anti-oxidant defenses and impaired autophagy (Figure 1). Addressing this pathway with anti-oxidants is a feasible and effective approach in preclinical models[33]. An alternative approach would be removal of dysfunctional mitochondria by enhancing autophagy. A target for enhancing autophagy is the enzyme mammalian target of rapamycin (mTOR), which is the key upstream regulator of autophagy. Activated mTOR prevents autophagy activation and its inhibition by rapamycin induces autophagy[34]. In genetically heterogeneous mice, rapamycin extended life span even when administration was initiated late in life, providing further support for the importance of autophagy in aging[35, 36].

In articular cartilage, autophagy is not only deficient in aging[31] but also in response to mechanical injury[37]. In an in vitro model, rapamycin treatment of cartilage explants that were exposed to high levels of mechanical load reduced cell death and extracellular matrix damage[37]. Rapamycin also suppressed biochemically induced cell death and nitric oxide production in response to proinflammatory cytokines. The first study to address potential therapeutic benefits of rapamycin in vivo used a knee instability-induced OA model in mice. Rapamycin treatment reduced the severity of OA and this was associated with preservation of cartilage cellularity[38]. These findings are the first to suggest that rapamycin is a promising new approach towards chondroprotection. Additional studies are required to directly link the rapamycin effects to removal of dysfunctional mitochondria and to analyze its efficacy in models of aging-related OA.

Chondroprotection through Lubrication

Articular cartilage functions as a surface that allows joint movement under conditions of extremely low friction. Hyaluronic acid (HA) and lubricin are two major joint lubricants and effective “boundary lubricants” that exhibit low friction and protect surfaces from wear[39]. Detailed mechanisms how HA is anchored and immobilized at the cartilage surface had not been established. Lubricin adsorbs to various types of substrates and forms complexes with itself and HA. Lubricin is thus expected to form cross-links with the surface-immobilized, partially entangled HA layer forming a cross-linked HA-lubricin complex. However, as the physical bond between HA and lubricin is relatively weak, it would be expected to dissociate under normal friction and shear forces[40]. The study by Greene et. al. examined mechanisms related to low friction and wear protection. Their results support a new concept of an adaptive mechanically controlled lubrication mechanism. According to this model, compression causes diffusion of nominally free HA out of the cartilage but then becomes

physically trapped at the interface by the increasingly constricted collagen pore network. The mechanically trapped HA-lubricin complex now acts as an effective chemically bound lubricant, reducing the friction force slightly, but more importantly, eliminating wear damage to the cartilage surfaces. This concept illustrates that the lubrication system as a whole requires both HA and lubricin to function optimally.

Besides their role in lubrication, both lubricin and HA have additional functions in the joint. Lubricin regulates synovial cell adhesion and proliferation. Lubricin mutations are linked to the camptodactyly-arthropathy-coxa vara-pericarditis syndrome, which features synovial hyperplasia and failure of joint function[41]. Mice that are deficient in lubricin not only show degradation of the cartilage superficial zone but also hyperplasia of intimal cells in the synovium. Purified or recombinant lubricin inhibits the synoviocyte proliferation in vitro[42]. Interestingly, a splice form of lubricin is a growth factor for endothelial cells[43]. Future studies will need to define in more detail the lubricin splice forms, their receptors and activities on cells involved in OA. A large number of studies already reported on cellular effects of HA, which include anti-inflammatory, cytoprotective and anabolic activities that are mediated by cell surface receptors CD44 and RHAMM[44, 45].

Both, HA and lubricin are deficient in arthritic joints[39]. Lubricin may be degraded and synthesis appears to be reduced, due to loss of joint lining cells, which are the main producers or due to inhibition of synthesis by inflammatory cytokines.

Based on the protective functions of HA and lubricin, their deficiency in arthritis joints and their synergistic activities, recent studies examined these molecules individually and in combination in animal models of joint injury and OA. Flannery et. al. reported that intraarticular injection of recombinant lubricin protected against cartilage degradation in a rat model of OA induced meniscectomy and medial collateral ligament transection[46]. Jay et. al. used the anterior cruciate ligament transection model in rats to compare three forms of lubricin, recombinant human lubricin, synovial fluid lubricin and lubricin produced by cultured synoviocytes[47]. Injected lubricin bound to the cartilage surface. All three forms of lubricin reduced the severity of cartilage damage but only the effect of lubricin from synoviocytes was statistically significant. Lubricin also protected against glycosaminoglycan depletion, collagen degradation and loss of cells in the cartilage superficial zone[47]. Teeple et. al. used the same OA model in rats to test lubricin purified from human synovial fluid and also compared it to and combined it with HA. These results confirmed the protective effect of lubricin but HA did not have protective effects and the therapeutic benefit of lubricin was enhanced by the addition of exogenous HA[48]. Previous studies on HA effects in OA models showed variable results, ranging from protective to deleterious effects[48].

These studies shed new light on the role of joint lubricants as potential OA therapies. The potential synergy between HA and lubricin suggested by molecular models has yet to be demonstrated in animal models. A specific clinical indication that appears to represent a promising opportunity for lubricants as therapeutics in posttraumatic arthritis, which is associated with an acute deficiency of lubricants[49].

Conclusions

These selected examples illustrate how progress in specific areas of biology can lead to identification of OA therapeutic targets, which can be readily validated in animal models. The findings from the past year add to an extensive list of OA drug candidates that were effective in animal models. A similar review in 2010 highlighted other signaling pathways in aging and the role of abnormal hypertrophic differentiation[50]. A major challenge in this field is how to select among these pathways and molecules the most promising candidates

for testing in clinical trials. The three examples discussed above represent distinct aspects of OA pathogenesis. Similarly diverse were the pathways that have been targeted in completed clinical trials, including inhibitors of matrix degrading enzymes, bone resorption or IL-1. Clinical trails with these drugs either failed to show conclusive efficacy or were associated with adverse events[51, 52]. These clinical results raise important questions in OA biology. Are drug targets valid and can methods be developed, for example based on systems biology approaches, to select or discover more promising drug targets? Do currently used animal models provide a meaningful representation of human OA? Are clinical trials design parameters in regard to patient risk factor profile and stage in the disease process appropriate? Can stages in the disease process and corresponding stage-specific interventions be identified? Should OA prevention and treatment start much earlier in the disease process than in previous studies? Answering these questions remains a challenge in OA biology and a prerequisite for the first successful clinical trial on a disease-modifying OA drug.

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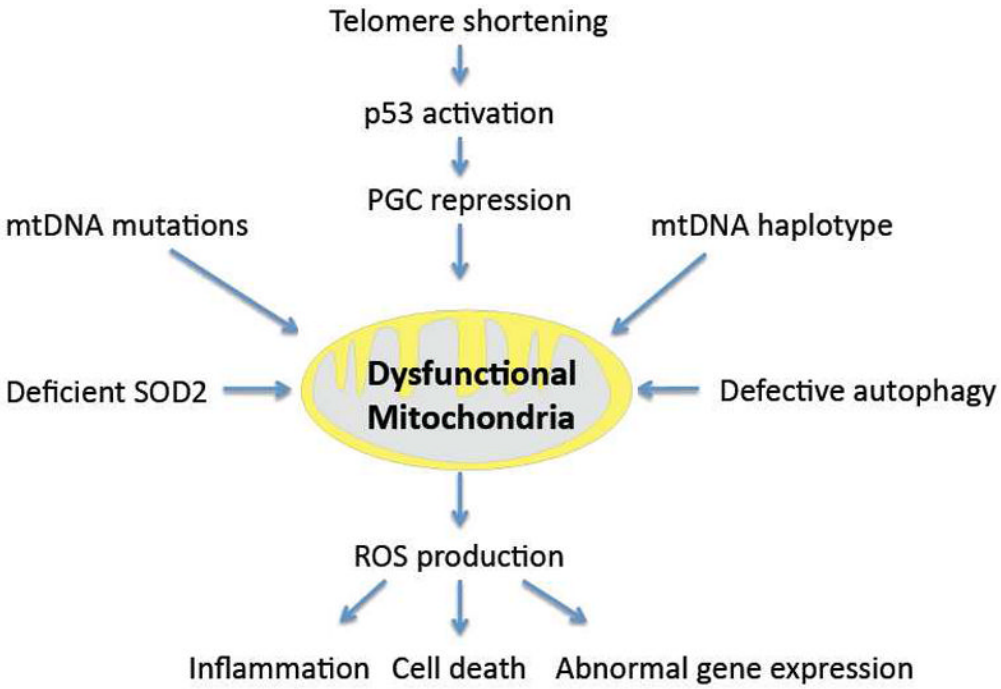

Fig. 1. Dysfunctional mitochondria in OA pathogenesis

Multiple factors contribute to mitochondrial dysfunction, including inhibition of mitochondrial biogenesis through suppression of key mitochondrial transcription factors PGC. Risk for mitochondrial dysfunction is also increased in individuals with certain mitochondrial DNA haplotypes and through acquired mitochondrial DNA mutations. As a result of defective autophagy, dysfunctional mitochondria accumulate and produce increased amounts of reactive oxygen species, which promote inflammatory responses, abnormal gene expression and cell death. The impact of mitochondrial dysfunction is further aggravated by reduced levels of SOD2 and deficient anti-oxidant defenses.