Special Article

Free Radicals in Primary Knee Osteoarthritis

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Free radicals have an important role in the pathogenesis of knee osteoarthritis. Reactive oxygen species (ROS) produced by abnormal chondrocyte metabolism exceeds the physiological buffering capacity and results in oxidative stress. The excessive production of ROS can damage proteins, lipids, nucleic acids, and matrix components. They also serve as important intracellular signaling molecules that amplify the inflammatory response. An understanding of oxidative stress involved in this disease might allow the use of antioxidant therapies in the prevention and/or treatment of knee osteoarthritis.

Keywords: *Osteoarthritis, Free radicals, Reactive oxygen species, Chondrocytes*

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Osteoarthritis (OA) is the most common form of joint disease that currently lacks effective treatment[1]. It is also the leading cause of disability among the elderly. It has been estimated that 68% of Americans (aged over 55 yr) and 35-46% of Thais (aged over 60 yr) have OA[2,3]. The economic burden attributed to the joint pain and disability of OA amounts to billions of dollars each year in the USA[4]. As the population demographic in the US and Thailand changes to one of a predominantly older generation, the increasing prevalence of OA will become a major public health problem. OA is a disease of a whole organ system including, the joint, the cartilage, the subchondral bone, the synovial capsule and membrane and the periarticular (connective and muscular) tissues. The metabolic and structural changes in the articular cartilage are thought to play a leading role in the initiation and the progression of the disease process. Articular cartilage is a highly specialized and uniquely designed biomaterial that forms the smooth, gliding surface of the diarthrodial joints. It consists mostly of an avascular, aneural and an alymphatic matrix which is synthesized by the sparsely distributed resident cells, the chondrocytes[5]. The extracellular matrix is extensively composed of collagens (mainly type II collagen) and proteoglycans (mainly aggrecans) that are responsible for the functional properties of cartilage. The adult articular cartilage is in principle working through the biomechanical properties of its extracellular matrix, and the destruction of the extracellular matrix of articular cartilage is the hallmark of OA. However, the chondrocytes play a decisive role as they are solely responsible for matrix turnover and maintenance. An imbalance between the destruction and synthesis of cartilage is thought to be an essential feature of OA cartilage degeneration[6,7].

As adult articular cartilage is an avascular and, thus, perse hypoxic tissue, the cells must be well adapted to this. The implications of this hypoxic environment are hardly understood on the molecular level. Additionally, the role of changes in oxygen (O_2) levels during the process of cartilage degeneration seems to be of great interest. Oxygen can also be processed into the so-called reactive oxygen species (ROS). ROS are molecules like hydrogen peroxide, (H_2O_2), ions like the hypochlorite ion (OCl^-), radicals like hydroxyl radical ($OH^\cdot$) or the superoxide anion ($O2^{-\cdot}$) which is an ion and a radical at the same time. ROS involved both in intracellular signaling for cell physiology, and in cellular destruction[8]. Therefore, this review is intended to give an overview of the role of oxidative stress only in primary knee osteoarthritis (knee OA). In the first part, we explained the reactive oxygen species and oxidative stress. The second part,

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we summarized the current evidences of oxidative stress in knee OA.

Free Radicals and Oxidative Stress

Free radicals and reactive oxygen species (ROS)

Free radicals can be defined as molecules or molecular fragments with an unpaired electron[9]. This unpaired electron usually gives a considerable degree of chemical reactivity to the free radicals. The typical reactions of free radicals are (a) electron donation (from a reducing radical) and electron acceptance (for an oxidizing radical) (b) hydrogen abstraction (c) addition reaction (d) self-annihilation reaction (e) disproportionations

Examples are:

(a) $HO^{\cdot} + RS^{-} \rightarrow OH^{-} + RS^{\cdot}$

(b) $CCl_3^{\cdot} + RH \rightarrow CHCl_3 + R^{\cdot}$

(c) $CCl_3^{\cdot} + CH_2 = CH_2 \rightarrow CH_2(CCl_3)\text{-}CH_2$

(d) $CCl_3^{\cdot} + CCl_3^{\cdot} \rightarrow C_2Cl_6$

(e) $CH_3CH_2^{\cdot} + CH_3CH_2^{\cdot} \rightarrow CH_2 = CH2 + CH_3\text{-}CH_3$

Because of the high reactivity of the unpaired electron in free radical molecules, they rapidly react to adjacent molecules such as DNA, protein, and lipids and cause alterations in their structures. Free radical molecules represent a living state from which oxygen-derived species such as superoxide ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), hydroxyl free radical ($OH^{\cdot}$), lipid peroxides, or related species can be easily generated, both intra- and extra-cellularly. Such agents cause various degrees of toxicity in cells and can lead to either transient or irreversible damage[8].

Physiological roles for ROS

ROS are produced during normal aerobic cell metabolism, have important physiological roles in maintaining cell redox status, and are required for normal cellular metabolism including facilitating intracellular signaling pathways and the activity of transcription factors such as NF-κB, activator protein 1, C-Myb, p53, and hypoxia-inducible factor-1α (HIF-1α) (10-12). In addition, ROS produced by phagocytes also seem to have important physiological roles in priming the immune system[13,14].

Cellular Oxidant defense mechanism to free radicals

An antioxidant can be most broadly defined as anything that inhibits an oxidative process. This includes the binding of potentially catalytic iron and copper, which can catalyze oxygen free radical production, in storage proteins. Antioxidants can inhibit oxygen free radical production by four mechanisms[15]:

(i) removing the transition metal catalyst
(ii) breaking chain reactions
(iii) reducing reactive species
(iv) scavenging initiating radicals

They do not act independently of one another but rather function co-operatively. The anti-oxidant has been introduced as a differentiation between primary and secondary antioxidant defense[16]. The former includes the activities of catalase, super-oxide dismutase, glutathione peroxidase, and DT-diaphorase, as well as small molecules such as ascorbic acid, α-tocopherol, GSH, β-carotein and uric acid. The latter includes proteolytic- and lipolyitc-enzymes[16], as well as the DNA-repaired systems[17]. Antioxidants are substances that compete effectively with other oxidizable substrates even when present in low concentrations, thereby protecting other substrates from the damaging effects of ROS.

Evidence for Oxidative Stress in Knee OA

Several lines of evidence suggest a role of oxidative stress in the pathogenesis of knee OA. Epidemiologic studies have shown an inverse association between dietary intake of antioxidant and OA progression[18-20]. A systematic review of randomized clinical trials by Canter et al (2007) also showed either positive or negative efficacy of both vitamin C and vitamin E in the treatment of knee OA[21]. Iron, a catalyst for hydroxyl radical production from hydrogen peroxide is present in both synovial tissue and synovial fluid of knee OA[22-24]. Several groups have demonstrated increased oxidative enzyme activity along with decreased antioxidant levels in knee OA sera and synovial fluids[25-29]. Because of the highly reactive nature of ROS, it is difficult to directly demonstrate their presence *in vivo*. It is considerably more practical to measure the 'footprints' of ROS, such as their effects on various lipids, proteins, and nucleic acids. Thus, evidence for oxidative stress or footprints in knee OA has in many cases been generated by approaches that detect oxidant-induced changes to these molecules. Studies of osteoarthritis cartilage and its synovial fluid have demonstrated oxidative damage to proteoglycan[30,31], lipid peroxidation products[32,33], and increased carbonyl groups reflective of oxidation damage to proteins[34]. Evidence of oxidative damage to cartilage, extracellular collagen, and intracellular DNA has also been demonstrated.

Generation of ROS in knee OA

Free radicals are formed disproportionately in

knee OA by abnormal chondrocytes metabolism[35-37]. Nitric oxide ($NO^{\cdot}$) and superoxide anion ($O_2^{\cdot-}$) are the two main ROS radicals can be produced by chondrocytes. These two highly reactive radicals can further produce the derivative radicals, peroxynitrite ($ONOO^-$) and hydrogen peroxide (H_2O_2), respectively[38]. The first radical, $NO^{\cdot}$ radicals, are synthesized by NO synthase (NOS) enzyme. *In vitro* studies demonstrated that there was an induction of NOS enzyme in chondrocytes culture cells[39,40]. The second radical, superoxide anion radicals are produced by the enzyme complex NADPH. Articular chondrocytes can produce superoxide anion by this enzyme system[41-43]. In the presence of ferrous iron, hydrogen peroxide and superoxide are converted via the Fenton reaction to highly reactive, aqueous soluble hydroxyl radicals by chondrocyte and cartilage[44]. Recently, it was reported that chondrocytes can synthesis the enzyme myeloperoxidase. It was suggested that chondrocytes can produce hypochlorous acid[45]. In addition, mechanical compression of chondrocytes can produce reactive oxygen species[46-49].

Effect of ROS on chondrocyte DNA

Chondrocyte senescence and cartilage ageing are now considered as an important factor contributing to the development of knee OA. The loss of cells is likely to be of multifactorial origin, with both necrosis and apoptosis being responsible[50,51]. Oxidative damage can initiate apoptosis through caspase activation and also may lead to irreversible growth arrest[52]. $NO^{\cdot}$ has long been considered as the primary inducer of chondrocyte apoptosis mediated by caspase-3 and tyrosine kinase activation[53,54]. However, it has become clear that NO by itself cannot initiate apoptosis and that the concomitant production of $O_2^{\cdot-}$ is required, suggesting the role played by $ONOO^-$ in this process[55].

Oxygen free radical induced genomic instability, including telomere instability and resulting in replicative senescence and dysfunction in human chondrocytes as demonstrated by Yudoh et al (2005)[31]. In tissue cultures of articular cartilage explants, lower antioxidative capacity and stronger staining of nitrotyrosine were observed in the degenerating region of knee OA cartilage as compared with the intact region. During continuous culture of chrondrocytes, telomere length, replicative capacity and GAG production were decreased by treatment with ROS. These effects could be corrected by treatment with an antioxidant agent. Grishko et al (2008) reported mitochondrial DNA damage and poor mitochondrial DNA repair capacity for removing damage caused by oxidative stress in isolated human articular cartilage from knee joint OA patients[56].

Effect of ROS on matrix protein synthesis

Exposure of the chondrocytes to H_2O_2 inhibits proteoglycan and DNA synthesis and depletes intracellular adenosine triphosphate (ATP) as a result of a simultaneous inactivation of glyceraldehydes-3-phosphate dehydrogenase[57,58]. Exogenous nitric oxide ($NO^{\cdot}$) has suppressive effects on the proteoglycan production. Both S-nitroso-N-acetyl-L, D-penicillamine (SNAP: a donor of $NO^{\cdot}$) and SIN-1(SIN-1,3 morpholinosydnimine: a compound generating both $NO^{\cdot}$ and $O_2^{\cdot-}$) are reversible and had an inhibitory effect on glycoaminoglycan synthesis[59,60]. Superoxide dismutase reverses SIN-1 inhibited GAG synthesis by primary bovine chondrocytes in a monolayer. Pre-treatment of chondrocyte with SIN-1 or $ONOO^-$ downregulates aggrecan gene expression, suggesting the involvement of $ONOO^-$ in the inhibition of aggrecan synthesis[61].

Effect of ROS on cartilage matrix breakdown

ROS may cause damage to all matrix components. Several in vitro studies have reported the degradation of cartilaginous tissue slices by ROS-generating systems. Damage is believed to be due to direct attack of proteoglycan and collagen molecules by free radicals. Incubation of soluble type I collagen with superoxide anion radicals generated by the xanthine oxidase-hypoxanthine system degrades collagen and prevents the formation of fibrils by this collagen[62,63]. $OH^{\cdot}$ can degrade collagen and modify the amino acid composition[64]. Type I collagen exposure to HOCl fails to degrade collagen but induces the formation of cross-links of an unknown nature[65]. HOCl also induces hyaluronic acid cleavage and reduces synovial fluid viscosity[66]. Recently, it was suggested that lipid peroxides could play a key role in the structural destabilization of cartilage matrix[32].

Conclusion

From these in vitro and *in vivo* studies, we can concluded that in knee OA conditions, ROS such as H_2O_2, $NO^{\cdot}$, $O_2^{\cdot-}$, and NO-derived nitrogen species contribute to cartilage degradation by inhibition matrix synthesis, by directly degrading matrix components and by inducing cell death. Altogether, these finding support the concept of antioxidant therapy to treat knee OA.

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อนุมูลอิสระในโรคข้อเข่าเสื่อมปฐมภูมิ

วีระศักดิ์ สุทธิพรพลางกูร, นพวรรณ ภู่มาลา มอราเลส, ทศศาสตร์ หาญรุ่งโรจน์

อนุมูลอิสระมีบทบาทสำคัญในกลไกการเกิดโรคข้อเข่าเสื่อม อนุมูลอิสระของออกซิเจนที่ผลิตจากเมตาบอลิสมที่ผิดปกติของเซลล์กระดูกอ่อนที่เกินจากภาวะปกติของร่างกายทำให้เกิดภาวะเครียดออกซิเดชั่น อนุมูลอิสระที่มากเกินปกติสามารถทำลายทั้งโปรตีน, ไขมัน, ดีเอนเอ และส่วนประกอบของผิวข้อ นอกจากนี้ อนุมูลอิสระยังส่งเสริมให้เกิดการอับเสบที่มากขึ้นโดยผ่านการสื่อสารภายในเซลล์ ดังนั้นการเข้าใจในภาวะเครียดออกซิเดชั่น ในโรคข้อเข่าเสื่อมอาจนำไปสู่การให้การป้องกัน หรือ รักษาโดยใช้สารต้านภาวะเครียดออกซิเดชั่นต่อไป