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Review

The emerging role of endothelin-1 in the pathogenesis of subchondral bone disturbance and osteoarthritis

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SUMMARY

Mounting evidence suggests reconceptualizing osteoarthritis (OA) as an inflammatory disorder. Trauma and obesity, the common risk factors of OA, could trigger the local or systemic inflammatory cytokines cascade. Inflammatory bone loss has been well documented; yet it remains largely unknown about the link between the inflammation and hypertrophic changes of subchondral bone seen in OA, such as osteophytosis and sclerosis. Amid a cohort of inflammatory cytokines, endothelin-1 (ET-1) could stimulate the osteoblast-mediated bone formation in both physiological (postnatal growth of trabecular bone) and pathological conditions (bone metastasis of prostate or breast cancer). Also, ET-1 is known as a mitogen and contributes to fibrosis in various organs, e.g., skin, liver, lung, kidney heart and *etc.*, as a result of inflammatory or metabolic disorders. Subchondral bone sclerosis shared the similarity with fibrosis in terms of the overproduction of collagen type I. We postulated that ET-1 might have a hand in the subchondral bone sclerosis of OA. Meanwhile, ET-1 was also able to stimulate the production of matrix metalloproteinase (MMP)-1 and 13 by articular chondrocytes and synoviocytes, by which it might trigger the enzymatic degradation of articular cartilage. Taken together, ET-1 signaling may play a role in destruction of bone-cartilage unit in the pathogenesis of OA; it warrants further investigations to potentiate ET-1 as a novel diagnostic biomarker and therapeutic target for rescue of OA.

Introduction

Osteoarthritis (OA) is the most common of age-related degenerative joint disorders. It is a leading cause of pain and disability among older adults. OA is a whole joint disorder with low-grade inflammation, afflicting articular cartilage, subchondral bone, synovium, ligaments and joint capsule. The hallmark of OA is the degradation of articular cartilage. The integrity of articular cartilage relies on the interplay with the other joint tissues, in particular subchondral bone[1]. On the basis of hypertrophic changes of subchondral bone such as osteophytosis and sclerosis, OA is differentiated from the other types of arthritis, e.g., rheumatoid arthritis (RA).

Recently, mounting evidence suggests that OA should be conceived as an inflammatory disease rather a simple wear-and-tear problem[2]. The complements system was found to play a central role in the initiation and deterioration of cartilage damages[2]. Joint trauma and incurred joint instability could activate local inflammatory response. Transforming growth factor-β1 (TGF-β1), a key inflammatory mediator, was activated at subchondral bone in response to anterior cruciate ligament transection (ACLT) to initiate the onset of OA in a mice model[3]. Obesity is a recognized risk factor of OA[4]. As part of metabolic syndrome (MetS), diabetes was also proposed as an emerging independent risk factor of OA[5]. We once observed a significant bone loss at subchondral plate in OA patients with the comorbidities, i.e., hypertension and diabetes[6]. Systemic inflammation is a hallmark of MetS. Inflammatory bone loss has been documented in RA[7], yet the biological link between inflammation and the disturbances at OA subchondral bone, in particular its hypertrophic or sclerotic changes, remains largely unknown.

Actually, osteoblasts derived from sclerotic bone of OA patients exhibited high profile of inflammatory cytokines including TGF-β1,

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prostaglandin E2 (PGE_2), interleukin-1β (IL-1β), interleukin-6 (IL-6) and *etc.*[8]. Amid a cohort of inflammatory cytokine mediators, endothelin-1 (ET-1) is known to mediate physiological and pathologic bone formation[9]. In addition, ET-1 has been implicated in the degradation of articular cartilage in either inflammatory or degenerative arthritis[10–15]. Meanwhile, high level of plasma ET-1 was also identified in the obese individuals and patients with hypertension and diabetes[16]. All data pointed in the direction that ET-1 could be one of candidate inflammatory factors to govern the hypertrophic changes of subchondral bone, as a sequel of local and systemic inflammation, in the pathogenesis of OA. We therefore aimed to identify the information gap regarding the role of ET-1 in OA subchondral bone disturbance by the integration and interpretation of the existing data about ET-1 signaling in inflammation, arthritis, the physiological and pathologic bone formation and *etc.* It would provide a new insight into molecular mechanism underlying the destruction of bone–cartilage unit and shed light on the discovery of therapeutic targets for OA.

ET-1, inflammation and fibrosis

ET-1, a 21-amino acid peptide, was first discovered as a potent vasoconstrictor in 1988[17]. It has two structurally similar G protein-coupled receptors, endothelin type A receptor (ETAR) and type B receptor (ETBR). It is received that ETAR is responsible for transducing the most of biological effects of ET-1 while ETBR serves primarily as a clearance receptor[18]. ET-1 is synthesized as preproET-1 that is cleaved to form the precursor big ET-1 or proET-1. Endothelin converting enzyme-1 converts big ET-1 to form the active peptide ET-1[19]. Big ET-1 only has 1/100 of the potency of mature ET-1. Extracellular conversion to ET-1 could elicit sufficient stimulus for biological processes subsequently[18].

ET-1 and nitric oxide (NO) act against each other to maintain vascular homeostasis and the balance of vasoconstriction and vasodilation[20]. Hypertension could be a result of the disturbed balance between ET-1 and NO[21]. The overexpression of ET-1 specifically in endothelial cells using *tie-1* promoter could lead to systemic hypertension with altered vascular reactivity in a mouse model[22]. A reduction of systemic blood pressure in patients with essential hypertension by ET-A receptor antagonists further demonstrated the link between ET-1 signaling and hypertension[23]. Moreover, insulin has been shown to induce ET-1 production at the transcriptional level[24], and ET-1 may involve in the vicious cycle of insulin resistance in the pathogenesis of diabetes[25].

Also, ET-1 may contribute to the complications of hypertension or diabetes such as the fibrosis of heart, lung, kidney and skin by activating the inflammatory and fibrotic signaling pathways[26,27]. The severity of fibrosis appeared in an association with the level of local ET-1[28]. Growing bodies of evidence suggested that ET-1 cooperated with TGF-β1, a known pro-fibrotic factor, in the pathogenesis of fibrosis in various tissues[29–31]. Blockade of endothelin signaling either pharmaceutically (ETAR or ETBR antagonists or neutralizing antibodies) or genetically (ETAR or ETBR siRNA) could decrease the secretion of TGF-β by fibroblasts and attenuate the fibrosis phenotype[26]. TGF-β1 also promoted ET-1 production in a Smad2/3-dependent fashion in skin fibroblasts[29]. In the fibrotic lung fibroblasts, TGF-β1 activates ET signaling through type I receptor and then downstream ALK5/c-Jun N-terminal kinase (JNK)/Ap-1 signaling that is independent of Smad proteins[30]. The dual ETA/ETB receptor antagonist, e.g., Bosentan, could interrupt the constitutive JNK activation in fibrotic fibrolasts, providing the evidence of an autocrine endothelin loop of ET-1 in its fibrotic effects. In addition, ET-1 may exert its fibrotic effects by activating a tissue factor/thrombin amplification loop, which is responsible for the production of connective tissue growth factor (CTGF)[31]. Last but not least, the endothelial mesenchymal transition (EndMT) process was also implicated in the ET-1-mediated fibrosis[32]. Taken together, targeting the axis of TGF-β1/ET-1 signaling is likely to be of benefit in battling with fibrotic disorders.

ET-1 and arthritis

ET-1 has been implicated as a major informatory mediator in various autoimmune diseases such as RA[33] and scleroderma[34] (Table I). It was reported that both local (synovial fluid) and systemic (serum) levels of ET-1 were significantly higher in RA patients than in healthy subjects[10]. Synovial macrophage-like cells could produce ET-1[35] that interacted with the other inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-1β to regulate the adhesion proteins production, e.g., intercellular adhesion molecule-1, vascular cell adhesion molecule-1, CD106 and CD44 in cultured synovial fibroblasts[36,37]. It supports a notion that ET-1 plays a role in the inflammatory responses of synovitis by recruiting neutrophil and endothelial cells to infiltrate the inflamed tissue in arthritis[38]. Moreover, the elevated level of local ET-1 was also linked up to the extra-articular manifestations of RA, e.g., hypertension[39]. IL-6, the most abundant pro-inflammatory cytokines in the serum and synovial joints of RA, could directly induce the preproET-1 mRNA expression in the fibrotic kidney with angiotensin II-induced hypertension[27].

ET-1 could exert its direct effects on articular chondrocytes as well as the synovial inflammation and fibrosis. Articular chondrocytes themselves rarely express ET-1 unless the natural aging process[13] or diseased conditions[14,15]. In addition, the expression level of ET receptors on articular chondrocytes was also affected by the age as well as various growth factors and cytokines including platelet derived growth factor-BB (PDGF-BB), TGF-α, TNF-α, IL-1β and *etc.*[40,41]. The ET-1- binding sites on articular chondrocytes were predominantly of ETAR[41]. The number of ET-1 binding sites on the aged chondrocytes was approximately twice as many as the

Table I
Endothelin signaling in various types of arthritis and other musculoskeletal disorders

Authors	Type of arthritis	Specimen	Findings
Nahir AM *et al.*[12]	RA, OA	Synovial fluid	Endothelin level in synovial fluid of RA was similar to in OA.
Haq A *et al.*[10]	RA	Serum and synovial fluid	ET-1 level in serum and synovial fluid of RA patients was higher than normal.
Yoshida H *et al.*[11]	RA	Synovial cells	Synovial macrophage-like type A cells could produce ET-1.
Iwabuchi H *et al.*[36]	RA, OA	Synovial fibroblasts	TNF-α up-regulated ICAM-1 in RA and OA fibroblasts while ET-1 inhibited this process.
Miyasaka N *et al.*[87]	Inflammatory arthritis	Synovial fluid	ET-1 in synovial fluid was higher than serum.
Roy-Beaudry M *et al.*[15]	OA	Articular chondrocyte	ET-1 induced MMP-1 and 13.
Manacu CA *et al.*[14]	OA	Articular chondrocyte	ET-1 caused NO, MMP1 and MMP13 overexpression.
Wei Yuan *et al.*[45]	Lumbar disc degeneration	Cells from endplate	ET-1 increased MMP-1 and MMP-13, decreased TIMP-1, and induced NO.

Abbreviation: ET-1, endothelin 1; RA, rheumatoid arthritis; OA, osteoarthritis; TNF-α, tumor necrosis factor-alpha; ICAM-1, Intercellular Adhesion Molecule 1; MMP-1/13, metalloproteinase 1/13; TIMP-1, tissue inhibitor of metalloproteinase-1.