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Caveolin-p38MAPK Signal Pathways：The Potential Molecular Targets for Osteoarthritis

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Abstract: Excessive inflammation is becoming accepted as a critical factor in osteoarthritis, one such tactic is the targeting of proteins involved in intracellular signal transduction to inhibit the excessive inflammation. The p38 mitogen-activated protein kinase (MAPK) signal pathways affect a variety of intracellular responses, with well-recognized roles in osteoarthritis, due to in vitro and in vivo evidence that this pathway is significantly involved in the pathogenesis of arthritis, it has been the focus of much attention in drug development in recent years, but inhibitors of p38 kinase have largely failed in clinical trials, due to both lack of efficacy and adverse events. In recent research, Caveolin-1 down-expression suppressed excessive inflammation-stimulated phosphorylation of p38 to inhibit the activity of p38MAPK signal pathways, In this review, we focus on the potential molecular targets of cavoelin-p38MAPK signal pathways for osteoarthritis, We summarize how this pathway has been exploited for the development of therapeutics and discuss the potential obstacles of targeting this pathway for the treatment of osteoarthritis.

Keywords: Osteoarthritis; Caveolin-p38MAPK; Signal Pathways

1. Introduction

Osteoarthritis (OA) is a slowly progressive degenerative disease of the joints that at present [1] increases in prevalence with age and is a major cause of pain, loss of functional independence, psychological impairment and a reduction in the overall quality-of life that affected nearly half of the elderly population [2]. The high prevalence of this disease results in high costs for treating patients, and therefore the development of good therapeutics for osteoarthritis is a matter of great urgency. With the aging of the ‘‘baby boom’’ population and increasing rates of obesity, the prevalence of OA is estimated to increase 40% by 2025 [3].

2. OA and its mechanism

OA is a multifactorial degenerative joint disease in which the cartilaginous matrix of the articular joint is destroyed and caused by interplay of genetic, metabolic, biochemical and biomechanical factors. The anabolic and catabolic imbalance in articular cartilage plays a crucial role in OA pathogenesis. As a result, enhanced degradation occurs in the macromolecular components including aggrecan and collagen. The character of OA is the degradation of articular cartilage and over-growth of cartilage and bone, known as osteophytes, at the periphery of the articular surface, and excessive inflammation which results in pain and loss of joint function [4]. Microscopically, loss of proteoglycan and fibrillation of the articular surface are observed at the early stage of arthritis. At later stages, clefts are formed, and at the end stage, erosive changes in the articular cartilage appear and results in pain, swell, malformation as the main symptoms [5].

The superficial zone of OA cartilage contains interleukin (IL)-1β, tumor necrosis factor-alpha

(TNF- α), and matrix metalloproteinases (MMPs) including MMP-1, 2, 3, 8, 9, and 13 [6]. IL-1 β an d TNF-α can induce chondrocytes to produce other cytokines as well as stimulate catabolic proteinases (MMPs or aggrecanases) and proinflammatory mediators such as nitricoxide (NO) and prostaglandin E2(PG E2) . NO is a crucial mediator of the inflammatory response by virtue of its physiological effects and its ability to regulate the expression of inflammatory proteins . In this way, they can alter compensatory biosynthetic homeostasis and break down the integrity of the ECM [7]. The disease progression and structural changes show that the over-production such as IL-1β , TNF- α and MMPs are central pathophysiological events in OA.

Recent studies have demnstrated that OA is regulated by the over-production above that can activate a broad array of intracellular signal transduction mechanisms [8]. The course of the disease is related to a number of complex pathways, MAP kinases are especially important

because they regulate the production of several mediators of inflammation and cartilage damage [9]. In OA cartilage, the level of phosphorylated MAPKs, p38MAPK pathway appears to be one of the most important pathways in cartilage. it can be specifically activates downstream to over-production of MMP-1, -3, and −13, TNF-α, and IL-1β [10]. However, the precise up and down-stream mechanism are unknown, which limits effective therapeutic interventions in OA. With these protease activities in mind, it is logical to target these actions to stop the progression of cartilage degradation in OA.

3. The P38MAPK and OA

P38MAPK is the most downstream signalling step before the transcription factor level and part of a greater family of proteins, the MAPKs, which share similar organisation structure. Other papers have previously described p38MAPK pathways [11]. P38MAPK was discovered in a pharmacological screen for the identification of compounds that modulate the production of TNF-α by lipopolysaccharide-stimulated human monocytic cells [12]. Since then, four isoforms of p38 MAPK(α, β, γ and δ) with >60% overall sequence homology and >90% identity within the kinase domains have been described in human tissues.

Inflammatory stimuli, such as lipopolysaccharide (LPS), TNF-α and IL-1 are the major inducers of p38MAPK.In G Schett"s research, there are three step of activation of p38mapk signal pathway, , the first step (activation of map kinase kinase kinases): Plasma membrane receptors are linked to the most upstream kinase (mitogen-activated protein kinase kinase kinase, MAPKKK or MEKK) in the by small GTPases of the ρ family, such as Ras, Rac, ρ or Cdc42 [13]. The second step: (activation of mapk kinases) Activation of p38MAPK is accomplished by mitogen-activated protein kinases kinases (MKKs), that phosphorylate p38MAPK at amino acid residues 180 and182. MKKs are themselves subject to phosphorylation by upstream kinases (MAP3Ks), through threonine and serine residues at a specific domain of the MKK. The type of MKK which ultimately leads to activation of p38MAPK and subsequent expression of proinflammatory mediators like IL-1 or IL-6 as well as matrix metalloproteinases depends on the initial trigger as well as on the cell types involved. The third step: activation of the p38 MAPK.

Although the important role of p38MAPK pathway in osteoarthritis is elucidated, there are many thing that remain unclear, such as The role of p38MAPK in the control of cell cycle and apoptosis, [14] whether the effect of reducing cartilage degradation is directly through p38MAPK-dependent regulation of MMP expression or an indirect effect due to lower expression of proinflammatory cytokines, especially IL1, which is a key inducer of MMPs and so on.P38MAPK has been a popular target for the design of anti-inflammatory drugs for well over a decade. More recently, a role for p38MAPK in migration, senescence, apoptosis, proliferation and differentiation suggests that modulation of the p38MAPK pathway could be of therapeutic benefit in a wider group of diseases

Due to in vitro and in vivo evidence that this pathway is significantly involved in the pathogenesis of arthritis, it has been the focus on much attention in drug development in recent years [15]. Since the first prototypical p38 inhibitor, SB203580, was identified in 1994 [16], numerous p38 inhibitors have been developed [17].

Traditional research opinion suggest that Mammalian p38s show similar roles and activation has been shown to occur in response to extracellular stimuli such as UV light, heat, osmotic shock, inflammatory cytokines(TNF- α & IL-1), and growth factors (CSF-1) [18]. And all of above factors can be proved in animal model, but the fact that Inhibitors of p38 kinase have largely failed in clinical trials, due to both lack of efficacy and adverse events will make ourselves-examination.

But should we ask why so many inhibitors of p38 kinase have largely failed in clinical trials of OA? May be the reason as below:

Tyler ZARUBIN [19] publishes an article show that this plethora of activators conveys the complexity of the p38 pathway and this matter is further complicated by the observation that activation of p38α is not only dependent on stimulus, but on cell type as well. Despite research that has shown that all four p38 group members display similar activation profiles [20], differences have been observed in the kinetics and level of activation of these isoforms. Furthermore, the activation of p38 isoforms can be specifically controlled through different regulators and coactivated by various combinations of upstream regulators. So there is increasing evidence that developing drugs to upstream regulators or downstream targets of p38MAPK might be more attractive than directly targeting p38MAPK or its isoforms [21]. Such approaches might be less toxic if targeting specific regulators or substrates that do not interact in feedback and crosstalk loops. Now appears Caveolin-1,

which is considered to be one of the upstream regulators of p38MAPK pathway in osteoarthritis.

4. Caveolin-1 and OA

Caveolin-1 acts as a scaffolding protein that concentrates and functionally regulates signaling molecules. Recently, great progress has been made toward understanding of the role of caveolin-1 in stress-induced premature senescence. Data show that caveolin-mediated signaling may contribute to explain, at the molecular level, how oxidative stress promotes the deleterious effects of aging and age-related diseases such as cellular senescence in osteoarthritis.

Caveolae are 50 to 100 nm flask-shaped invaginations of the plasma membrane enriched in cholesterol and glycosphingolipids. Caveolae can exist as individual invaginations or can be found in detached grape-like clusters and long tubular structures derived from the fusion of single caveolae. Caveolin-1 is a structural protein component of caveolae in most cell types [22].

Articular chondrocyte senescence is believed to contribute to the increased incidence of osteoarthritis with increasing age and catabolic stresses such as cytokines and oxidative stress have been shown to mediate the pathogenesis of osteoarthritis [23]. Interestingly, both IL-1β and hydrogen peroxide up-regulate caveolin-1 mRNA and protein expression and induce premature senescence in articular chondrocytes. Down-regulation of caveolin-1 expression with antisense oligonucleotides significantly prevents the induction of chondrocyte senescence induced by IL-1β and hydrogen peroxide [24], suggesting that caveolin-1 may play a role in the pathogenesis of osteoarthritis by mediating chondrocyte senescence, so chondrocyte senescence, inflammatory cytokines interact each other and became vicious circle in osteoarthritis. The importance of caveolin-1 in replicative senescence was also supported by studies showing that upregulation of caveolin-1 positively correlates with shortening of chondrocyte replicative lifespan after treatment with interleukin IL-1β [25].

5. Caveolin-1 expression and P38-MAPK Pathway

As described above, up regulation of caveolin-1 expression and P38-Makp signal pathway are all play a central role in osteoarthritis. What is the relationship between caveolin-1 and P38-Makp signal pathway? Studies show that caveolin-1 expression in senescent cells is regulated by p38 -MAPK. Signaling studies demonstrate that the p38MAPK is the upstream regulator of the caveolin-1 promoter following oxidative stress. Inhibition of p38 MAPK inhibits the upregulation of caveolin-1 protein expression and development of premature senescence [26].

These studies detail at the molecular level bring new insights into osteoarthritis, in other word,

whether caveolin-1 could activate p38MAPK pathway in osteoarthritis. Some studies show that consistent with these data, the Caveolin 1 overexpression induced p38 MAPK activation and impaired the ability of chondrocytes to produce type II collagen and aggrecan.

6. Conclusion

Data suggest that Inflammatory cytokines, cellular senescence and MMPS are contribute to osteoarthritis. Study above showed that up regulation of caveolin-1 expression and P38-Makp signal pathway are all play a central role in osteoarthritis, and two of them interact each other, with the increases of OA in the world, the effectively drug became urgent. Due to in vitro and in vivo evidence that p38-Mapk pathway is significantly involved in the pathogenesis of arthritis, it has been the focus of much attention in drug development in recent years but inhibitors of p38 kinase have largely failed in clinical trials, despite this rather disappointing track record, ongoing interest in other p38 kinase inhibitors has led to continuing clinical research in this area. There is increasing evidence that developing drugs to upstream regulators or downstream targets of p38MAPK might be more attractive than directly targeting p38MAPK or its isoforms, like caveolin-1, upstream regulators or downstream targets of p38MAPK, which may exploit the new light for the treatment of osteoarthritis.

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