Experimental Cell Research 359 (2017) 1–9

Contents lists available at ScienceDirect

Experimental Cell Research

journal homepage: www.elsevier.com/locate/yexcr

Small molecule therapeutics for inflammation-associated chronic musculoskeletal degenerative diseases: Past, present and future

Yangwu Chen[a,b,c,d,e], Jiayun Huang[a,b,c,d,e], Chenqi Tang[a,b,c,d,e], Xiao Chen[b,d,e], Zi Yin[b,d], Boon Chin Heng[f], Weishan Chen[a,c,*], Weiliang Shen[a,b,c,d,e,*]

[a] Department of Orthopedic Surgery, 2nd Affiliated Hospital, School of Medicine, Zhejiang University, Zhejiang 310009, China
[b] Dr. Li Dak Sum & Yip Yio Chin Center for Stem Cell and Regenerative Medicine, Zhejiang University, Zhejiang 310000, China
[c] Orthopaedics Research Institute of Zhejiang Univerisity, China
[d] Department of Sports Medicine, School of Medicine, Zhejiang University, Zhejiang 310000, China
[e] China Orthopaedic Regenerative Medicine (CORMed), Hangzhou, China
[f] Faculty of Dentistry, Department of Endodontology, The University of Hong Kong, Pokfulam, Hong Kong

ARTICLE INFO

Keywords:
Chronic musculoskeletal degenerative diseases
Inflammation
Small molecule
Signaling pathways
Osteoarthritis
Tendinopathy

ABSTRACT

Inflammation-associated chronic musculoskeletal degenerative diseases (ICMDDs) like osteoarthritis and tendinopathy often results in morbidity and disability, with consequent heavy socio-economic burden. Current available therapies such as NSAIDs and glucocorticoid are palliative rather than disease-modifying. Insufficient systematic research data on disease molecular mechanism also makes it difficult to exploit valid therapeutic targets. Small molecules are designed to act on specific signaling pathways and/or mechanisms of cellular physiology and function, and have gradually shown potential for treating ICMDDs. In this review, we would examine and analyze recent developments in small molecule drugs for ICMDDs, suggest possible feasible improvements in treatment modalities, and discuss future research directions.

1. Introduction

1.1. Definition of ICMDDs

Musculoskeletal diseases are pathological conditions that afflict muscle, bone, cartilage, joint, ligament, tendon, and other connective tissue. It is common in our daily life. The risk of developing musculoskeletal diseases usually increases with age, a large portion of which manifest degenerative pathological processes and is often associated with inflammatory signal changes during disease occurrence and progression [1–3]. Here, we term this as inflammation-associated chronic musculoskeletal degenerative diseases (ICMDDs). According to their definition and pathology, diseases like osteoarthritis, tendinopathy, and intervertebral disc degeneration (including but not limited to) can be classified as ICMDDs. The chronic musculoskeletal condition is considered as the primary cause of morbidity and disability, resulting in heavy socio-economic burden [4,5]. The major clinical symptoms of ICMDDs are characterized by pain, swelling, and limitations on mobility and physical activity. However, the absence of these symptoms during the early disease stages and ignorance of the affected population often makes early diagnosis difficult [6,7]. Consequently, when increasingly serious activity-related pain and lost physical function drive patients to seek medical assistance, ICMDDs usually have progressed into the middle or even late stages.

1.2. Current therapy

At present, the conservative non-surgical therapeutic options available to patients suffering from ICMDDs consist of activity modification, physiotherapy, non-steroidal anti-inflammatory medications (NSAIDs), and topical injections. Although these therapeutic modalities may offer some symptomatic relief in the short term, patients usually do not achieve definitive disease resolution [8,9]. Surgery is only recommended for those who have shown no remission after receiving these conservative treatment modalities, but the high rate of complications and ambiguous curative effects prevent it from being a routine measure [9,10]. Recently, there are two interesting studies that suggest moderate physical activity together with a diet rich in extra-virgin olive oil are beneficial for preventing cartilage degradation [11,12]. Nevertheless, there are neither effective nor evidence-based treatments for ICMDDs that have been applied in clinical practice, because the insufficient systematic research data on disease molecular

* Corresponding authors at: Department of Orthopedic Surgery, 2nd Affiliated Hospital, School of Medicine, Zhejiang University, Zhejiang 310009, China
E-mail addresses: chenweishan@zju.edu.cn (W. Chen), wlshen@zju.edu.cn (W. Shen).

http://dx.doi.org/10.1016/j.yexcr.2017.07.027
Received 11 May 2017; Received in revised form 19 July 2017; Accepted 21 July 2017
Available online 22 July 2017
0014-4827/

mechanisms makes it difficult to exploit valid therapeutic targets. By understanding the molecular mediators that result in degeneration of the musculoskeletal system, novel therapeutic targets for drug development could potentially be identified.

1.3. Advantage of small molecule drugs

Small molecule drugs are therapeutics with molecular weights of 600D or less, and can specifically target intracellular molecules [13]. By acting on specific signaling pathways in cell physiology and function, small molecules can modulate signaling transduction and gene transcription [13]. Although growth factors are also promising in ICMDDs treatment due to their ability to modulate cell physiology and function during tissue development [14], their immunogenicity is a significant limitation to clinical applications [15]. In contrast, the immune response in the host is negligible for small molecules because of their small size [16]. Moreover, small molecules can be administered orally, and they can be absorbed directly by the human body. Additionally, since macromolecular drugs strongly depend on their stereospecificity, they would lose efficacy and specificity if their complex three-dimensional forms are altered with the ever-changing external environment. But this eventuality will not be a problem for the majority of small molecules. Last but not least, small molecules are easy to synthesize, purify and produce in mass quantities. In fact, small molecule drugs have been widely used in the field of cancer therapy. For instance, the tyrosine kinase inhibitors, gefitinib and imatinib, have been used widely in the clinical treatment of non-small-cell lung cancer and chronic granulocytic leukemia, respectively [17,18]. Therefore, small molecules with therapeutic potential may be utilized to treat ICMDDs.

2. Methods

The literature search was performed on MEDLINE from inception to May 2017. No language restrictions are imposed. The search terms are as follows: ("Tendinopathy"[Mesh] OR "Tendon Injuries"[Mesh] OR "Osteoarthritis"[Mesh] OR "Intervertebral Disc Degeneration"[Mesh] OR "Discitis"[Mesh]) AND (signal* OR pathway*) AND ("Drug Therapy"[Mesh] OR "Small Molecule Libraries"[Mesh]). Inclusion criteria: experimental articles with originality, reliability and with the main content being highly relevant to our review. Exclusion criteria: articles that were not available online or have not been published. We initially screened the literature that met our requirements by reading the abstract. A total of 149 articles were identified, with 35 of these meeting the inclusion criteria. Reference lists of identified papers were searched manually for additional studies. This review article is written in the narrative form.

3. Small molecule drugs for ICMDDs

3.1. Small molecule drugs for osteoarthritis

3.1.1. Pathogenesis of osteoarthritis

Osteoarthritis (OA) is a common joint disease worldwide, afflicting about 14% of the world population over 60 years of age [19]. It is a complicated condition affecting the entire joint. The pathological changes in cartilage, subchondral bone, and synovium are all involved in the development of OA. The structural proteins of cartilage consist of type 1 collagen (COL1), aggrecan and other proteoglycans [2]. The former mainly provides cartilage with tensile strength, while the latter two provide compressive resistance [2]. In response to changes in the chemical and mechanical environment, chondrocytes are the most active component of the joint that regulate and maintain cartilage architecture and biochemical composition. Once activated, chondrocytes would produce cytokines and matrix-degrading enzymes, including matrix metalloproteinases (MMPs), disintegrin and metalloproteinase with thrombospondin-like motifs (ADAMTS). A series of chain reaction will finally generate severe pathological effects. It was also reported that cartilage destruction led to decreased expression of a newly-identified chondrocyte biomarker lubricin [20,21]. Similar to chondrocytes, osteoblasts and synoviocytes could release inflammatory mediators and degradative enzymes in subchondral bone and synovium, respectively [22]. A study shows that this biological process is secondary to an initial insult to the joint, and will drive progressive joint degeneration by further activating chondrocytes [23].

3.1.2. Wnt/β-catenin signaling pathway

Interleukin-1β (IL-1β) and tumor necrosis factor (TNF-α) can activate cydooxygenase-2 (COX-2), increase prostaglandin E2(PGE2) production, which in turn lead to joint pain and inflammation [24]. IL-1β and TNF-α are also capable of suppressing the expression and accumulation of articular cartilage extracellular matrix (ECM) constituents. The more severe these catabolic changes are, the faster the OA associated loss of cartilage matrix will be. It is critical to understand the role that Wnt/β-catenin signaling plays in IL-1β and TNF-α induced upregulation of MMPs activity [25]. Ellie et al. [26] found that IL-1β and TNF-α induced cartilage degradation in mice could be prevented completely by the small molecule PKF115-584 and partially by CGP049090, through inhibition of the WNT/β-catenin signaling pathway. SM04690, another small molecule inhibitor of the Wnt pathway, was shown to induce MSCs to differentiate into chondrocytes, block IL-1β induced production of TNF-α and IL-6, inhibit protease production, and eventually alleviate cartilage degeneration in a rodent model of OA [27]. Hinokitiol is a natural compound that has a broad range of biochemical and pharmacological activities [28]. Li et al. [29] demonstrated that hinokitiol could significantly inhibit MMPs expression induced by IL-1β in chondrocytes and ameliorate cartilage degeneration through morphological and histological analyses in vivo. The anti-inflammatory effect of hinokitiol is also brought about by Wnt/β-catenin signaling pathway inhibition [29]. Additionally, it is reported that hypoxia-inducible factor-1α (HIF-1α) is essential for maintaining homeostasis and regulating differentiation in articular chondrocytes [30]. By using conditional knockout mice (HIF-1α-/-), Bouaziz et al. [31] found that loss of HIF-1α could increase MMP-13 expression and aggravate cartilage destruction through regulation of Wnt signaling; while PKF118-310, an inhibitor of Wnt/β-catenin pathway, could reverse this pathological effect [31]. This study thus provides a novel insight into the role of HIF-1α in OA and reveals the link between the HIF-1α and Wnt/β-catenin pathway.

3.1.3. NF/κB signaling pathway

In addition to the Wnt/β-catenin signaling pathway, the biological effects of IL-1β and TNF-α on chondrocytes, including increased synthesis of MMPs, COX-2 and nitric oxide (NO), are also partially mediated by NF-κB [24,32]. Shikonin is the main ingredient of root extracts of a traditional herb. It has been reported that shikonin exert anti-inflammatory effects by inducing accumulation of high levels of IκBα protein in macrophages [33]. IκBα, the natural inhibitor of NF-κB present in cells, could suppress nuclear translocation of the p65 subunit of NF-κB and its phosphorylation. Li et al. [34] found that upregulation of MMPs and downregulation of tissue inhibitor of metalloproteinase-1 (TIMP-1) were ameliorated by treatment with shikonin at both the transcriptional and translational level in a rabbit OA model. In chondrocytes, they observed that shikonin ameliorated the reduction of IκBα induced by IL-1β [34]. Shakibaei et al. [35] noted that upon treating chondrocytes with curcumin, a compound extracted from turmeric; IL-1β induced NF-κB activation could be suppressed by curcumin's inhibitory effect on IκBα degradation. With the inhibition of the NF-κB signaling pathway, its downstream targets such as COX-2 and MMP-9 would be subsequently down manner regulated [35]. Resveratrol is isolated as a constituent of the roots of white hellebore. It can block NF-κB activation induced by TNF-α and IL-1β in a dose-dependent and time-dependent [36]. Shakibaei et al. [37] provided