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Editorial

Addressing musculoskeletal diseases by exploring the potentials of stem cells and plant-derived chemicals

Musculoskeletal diseases are challenging medical conditions which cause huge economic losses every year. Considering that many musculoskeletal disorders lack effective relief or recovery methods, it is essential to investigate novel strategies and the underlying mechanisms for these diseases. In this issue, we have included publications on the latest advances in stem cells and drug development for some challenging musculoskeletal disorders, as well as the mechanisms of those approaches.

Stem cells play vital roles in both tissue repair and degeneration. To enhance stem cell migration and chondrogenesis, Sun et al. used the static magnetic field for osteoarthritis (OA) treatment [1]. In pathological conditions, mesenchymal stem cells (MSCs) respond to the inflammatory environment and exert immunomodulatory effects. As an example, the roles of MSCs and macrophages in tendon-bone insertion injury and healing were explored to better understand their critical functions [2]. Tendon-bone structure regeneration is also key to rotator cuff healing, and Tong et al. facilitated rotator cuff healing by mediating bone marrow MSCs using exosomes derived from $CD133^{+}$ human urine-derived stem cells [3]. Chen et al. also utilized exosomes from human adipose-derived stem cells to treat intervertebral disc degeneration (IDD), founding that exosomal miR-155-5p promotes autophagy and reduces pyroptosis of nucleus pulposus cells [4]. Pyroptosis represents a form of cell death, and it is triggered by pro-inflammatory signals. Pyroptosis was reported to be involved in OA as well. The latest mechanism study demonstrated that pyroptosis as well as NLRP3 inflammasome response could be inhibited by liner ubiquitination of LKB1, which ameliorated OA [5]. Apart from pyroptosis, ferroptosis is another cell death form that is triggered by a large amount of iron accumulation and lipid peroxidation. Zhao et al. discovered that Forkhead box O3 attenuates OA by suppressing ferroptosis [6].

It is believed that the decreased osteogenic differentiation ability of MSCs is one of the most important reasons for senile osteoporosis. Therefore, Zhang et al. managed to enhance the osteogenic differentiation potential of MSCs by overexpressing microtubule actin crosslinking factor 1 (MACF1) and activating TCF4/miR-335-5p signaling pathway [7]. As Chen and Zhang's studies demonstrate the important roles of miRNAs in regulating musculoskeletal disorders, Hadjiargyrou et al. further investigated the miRNAome in human fracture callus and nonunion tissues, aiming to identify specific miRNAs involved in normal physiological fracture repair as well as those of nonunions [8]. These studies demonstrate that stem cells, cell death regulations, and miRNAs are potential therapeutic targets for musculoskeletal disorders.

Nerves are important for the musculoskeletal system since they support body motion and transmit sensory signals like pain for the diseases of IDD, OA, etc. Many patients suffer from these diseases because of sustainable pain. Zheng et al. investigated the mechanism of discogenic pain during IDD and found Netrin-1 as a mediator for nerve innervation and angiogenesis, which trigger pain [9]. Fortunately, the nervous system has a self-repair mechanism. Li et al. found that when the spinal cord is injured, cerebrospinal fluid-derived extracellular vesicles are able to promote vascular regeneration [10]. These studies give us a hint on pain relief strategy, which will largely elevate the life quality of patients.

Drugs addressing musculoskeletal diseases are also explored in this issue. Inspired by Traditional Chinese Medicine, Wang et al. analyzed the functions and mechanism of kaempferol from *Eucommia ulmoides* Oliver, or Du Zhong, in IDD [11]. Besides, Lu et al. investigated Physalin A from another plant *Physalis alkekengi* var. Franchetii, and validated its anti-inflammatory and anti-fibrotic effects in the same disease [12]. Pang et al. explored the tumor-suppressive effects and mechanism of gallic acid, which is enriched in various food and herbs, on osteosarcoma [13]. These studies provide promising candidates for the corresponding diseases. However, the side effects of drug administration should be noticed. Medication-related osteonecrosis of the jaw (MRONJ) is a severe complication associated with antiresorptive medications managing osteoporosis, such as bisphosphonates (BPs). Zhu et al. documented the effects of discontinuation of BPs before dental extraction in osteoporotic conditions [14]. Some drugs are also used to build animal models of diseases including methylprednisolone and dexamethasone, as Li et al. reviewed in the advances of osteonecrosis experimental models, together with other traumatic and non-traumatic methods [15]. Wang et al. explored if dexamethasone-induced muscle atrophy is an alternative model for the naturally aged sarcopenia model [16]. These studies show the therapeutic and animal model-establishing potential of plant-derived chemicals and other drugs.

We anticipate that this issue will provide researchers and clinicians valuable insights into the challenges that musculoskeletal diseases pose, as well as novel strategies to investigate and treat these diseases.

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