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EDITORIAL

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We are excited to launch the January 2023 issue of the Journal of Orthopaedic Translation. This issue contains 25 articles that cover basic, preclinical and translational research on musculoskeletal diseases and disorders, including osteoarthritis, osteoporosis, fracture, intervertebral disc degeneration, rotator cuff tear and sarcopenia. It is our hope that findings from these studies will improve our understanding of pathogenesis of these diseases and may provide relevant therapeutic strategies.

Osteoarthritis (OA) is a whole-joint multifactorial joint disease, which affects the articular cartilage, synovium and subchondral bone. There is no cure for OA. Current treatment focuses at reducing pain and improving joint function. Hsueh et al. revealed that the cell-extracellular vesicles from induced pluripotent stem (iPSC-EVs) ameliorated OA-like lesions, including inflammation, subchondral bone protrusion, and articular cartilage destruction, in the rabbit ACLT OA model. iPSC-EV increased chondrocyte proliferation and suppressed cell senescence. Furthermore, iPSC-EVs promoted ECM anabolism and inhibited its catabolism. These findings suggest that iPSC-EVs can be potentially used for OA treatment [1]. Numerous natural compounds have been tested for their potential anti-OA activity. In this issue, Wu et al. investigated the anti-inflammatory effects of stevioside (STE), a naturally diterpenoid glycoside, in OA treatment both in vitro and in vivo. They found that STE displayed marked chondroprotective effect and attenuated the development of OA in part via regulation of the Nrf2/HO-1/NF-κB signaling pathway [6]. Likewise, Li et al. showed that another anti-inflammatory drug 5-aminosalicylic acid (5-ASA), a first-line drug for ulcerative colitis, displayed a pro-anabolic effect on human chondrocyte pellet and osteochondral explant inflammatory OA models [18]. Zhu and coworkers revealed that metformin, an adenosine 5′-monophosphate-actived protein kinase (AMPK) activator, inhibited the phosphorylation of β-catenin^{S552} in primary chondrocytes and in articular cartilage, suggesting that metformin exerts its chondro-protective effect at least in part through the inhibition of β-catenin signaling, whose activation is known to induce OA lesions, in chondrocytes [16]. Osseointegrated implants for patients with transfemoral amputations are a novel treatment under development; but their prospective long-term evidence is lacking. In a prospective ten-year cohort study of patient-reported outcomes (PRO) and complications, Hagberg et al. showed that PROs were improved after the introduction of a novel principle for bone anchorage of amputation prostheses. However, an increasing rate of mechanical complications was of concern [7]. While the teriparatide (PTH (1–34)) is a potent bone anabolic drug for osteoporosis, it also exhibited marked chondroprotective effect in the study by Li et al. They showed that PTH (1–34) ameliorated articular cartilage degradation and aberrant subchondral bone remodeling in destabilization of the medial meniscus (DMM) induced OA mouse model [21]. The study by Liu and colleagues in this issue highlighted the importance of preclinical assessments of potential nanoparticles produced by wear and tear of metal implants using in vitro macrophage culture and in vivo animal models. They found that the combination of cobalt, chromium and titanium nanoparticles was more cytotoxic than any of the individual metals in vitro and induced higher expression of genes encoding pro-inflammatory cytokines than single metals in vivo. The in vivo model utilized in this study may provide a useful tool for rapid assessment of the effects of unintended release of metal nanoparticles from implants in pre- and post-marketing studies [12]. Aseptic loosening of the femoral stem after total hip arthroplasty (THA) is one of the most common causes of implant failure. Stress shielding (SS) is the main mechanical factor leading to aseptic loosening. Liu et al. showed that an auxetic femoral stem reduced SS after THA. The novel solution provided in this study may serve to increase the survival rate of femoral stems by reducing SS after THA [10]. Cartilage regenerative mechanisms initiated by knee joint distraction (KJD) are incompletely understood. Teunissen et al. reported that a catabolic-to-anabolic shift was observed in the canine osteoarthritic cartilage at 10 weeks of follow-up after KJD treatment. Further investigation of this time point and the pathways involved might elucidate the regenerative mechanisms behind KJD and improve the existing KJD treatment [13]. Total talar replacement (TTR) using a customized talus prosthesis is an emerging surgical alternative to conventional total ankle arthroplasty (TAA) for treating ankle problems. Chen et al. compared the influences of the two methods on foot biomechanics during gait using dynamic finite element analyses. They showed that the TTR better reproduced the foot joint motions, segment movements, and plantar pressure map of an intact foot during walking and thus could be a prospective surgical alternative for pathological ankles from a biomechanical perspective. Nevertheless, TAA reduced ankle mobility and increased movement of the adjacent joints and forefoot plantar pressure [8].

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Even with the availability of both anti-resorptive and anabolic drugs, osteoporosis (OP), which is characterized by low bone mass and high risk for fracture, is a major public health problem impacting a large population worldwide. In this issue, Huang et al. demonstrated a protective effect of melatonin on the bone loss in estrogen-deficient rats by suppressing adipose tissue accumulation in the bone marrow. Melatonin promoted osteogenic differentiation of the bone marrow stromal cells (BMSC) from ovariectomized rats by increasing RUNX2 expression while decreasing adipogenic differentiation by suppressing PPARγ expression through SIRT1 signaling pathway. These results suggest that melatonin can be potentially used for OP treatment by balancing osteogenesis and adipogenesis of BMSCs [4]. Yang et al. revealed that mice lacking the mixed lineage kinase 3 (MLK3) displayed a low bone mass and defective fracture healing with impaired osteoblast differentiation and MAPK activation [5]. In a randomized, double-blind, placebo-controlled, multicenter phase III study, Gu et al. showed that LY06006 (subcutaneously, every 6 months for one year), a denosumab biosimilar, significantly increased the bone mineral density of the lumbar spine, total hip, femoral neck, and femoral trochanter in Chinese postmenopausal osteoporosis women. LY06006 was well tolerated, and no unexpected adverse effects occurred. Thus, LY06006 might be an effective treatment for osteoporosis [2]. Zhang et al. showed that 1–2 T static magnetic field combined with iron oxide nanoparticles prevented unloading-induced bone loss in mice by regulating iron metabolism in osteoclastogenesis. The combined treatment strategy could better resist to unloading-induced bone loss in mice than separate treatment [9]. Liu et al. used SDSSD (an osteoblast-targeting peptide) to modify the natural compound geniposidic acid to improve its ability to promote bone formation. They found that modified compound was enriched into osteoblasts and promoted bone formation and effectively treated osteoporosis in mice at relatively low doses [11]. The frequently used anti-inflammatory drug glucocorticoid (GC) causes bone loss with poorly defined mechanism. Yuan et al. found that PINK1 (PTEN-induced putative kinase 1)-mediated mitophagy promoted the production of cathepsin K in osteocytes and thereby the extracellular matrix degradation, thus mediating the GC-induced bone loss [14]. Osteogenesis imperfecta (OI) is a congenital disorder characterized by muscle defect and skeletal fragility, and no cure is yet available. Sun et al. found that Irisin, a secreted myokine, effectively reduced bone fracture and attenuated bone abnormalities in the oim/oim OI mouse model by promoting osteogenesis and counteracting TGF-β/Smad signaling. These findings provided evidence for using Irisin as a potential therapeutic reagent to prevent the progression of OI [15]. Zhang et al. constructed an engineered bionic periosteum with a double layer of cells (the outer layer is blood vessel cells, the inner layer is osteoblast cells), which facilitated the repair of skull defects and promoted bone regeneration in rats [17].

Intervertebral disc (IVD) is a fibrocartilaginous structure consisting of the central nucleus pulposus, the peripheral annulus fibrosus and the cartilaginous endplates. IVD degeneration causes low back pain. Sun et al. used the single-cell RNA sequencing technology to reveal two subpopulations of annulus fibrosus (AF) cells in rats which displayed stemness and vascularization-inducing potential. respectively. The existence of these cell subpopulations was further validated in human AF [22]. Lumbar interbody fusion (IF) is a common procedure for obtaining spinal fusion by replacing the disc with an intervertebral cage. Duits et al. provided basic principles for species selection and practical guidelines for surgical procedures in a goat animal model. Information from this study will improve methodological rigor and documentation of future experiments [19]. Clinical examinations of scoliosis often include X-rays. Grünwald and coworkers presented a 3D body scanner image analysis tool that allowed orthopedic specialists to visualize and inspect patients' specific spinal deformations. This method was designed to provide complementary information on the Cobb angle for the assessment of spinal deformations in clinical routine. It may reduce X-rays follow-up examinations [3].

Sarcopenia is an age-related disease that increases the risk of falls and fractures in older adults. Ge et al. showed that the serum soluble interleukin 2 receptor (sIL2R) was an independent risk factor for sarcopenia and low muscle strength in men. sIL-2R has the potential to be developed as a diagnostic marker for sarcopenia and low muscle strength in elderly men at high risk of fracture [20]. The postoperative failure rate of rotator cuff tear (RCT) is still high due to the poor healing of the bone-tendon interface. Tong et al. showed the positive effect of lymphangiogenesis in promoting rotator cuff healing, suggesting that improving lymphatic drainage may be a new therapeutic approach to repairing the bone-tendon interface [25]. After analyzing 17 preclinical studies with SYRCLE's tool, Liu et al. revealed that the skeletal muscle was involved in the mediation of cognitive function. The secretory muscle factors, muscle atrophy or injury, and muscle-targeted treatments could alter the number of neurons, functional factors of the brain, and other AD pathological characteristics in mice [23].

Finally, in this issue, Chan et al. discussed a template to develop humanized technologies that meet true clinical needs. They emphasized the importance of integrating people, ideas, resources and technology, through keen observation, to develop humanized clinical technologies. Dehumanized R&D will not be successful [24].

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