Journal of Orthopaedic Translation 47 (2024) A1–A2

Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

Editorial

Understanding pathophysiology and injury mechanisms is the foundation for invention/innovation and clinical translation in orthopaedics

Aging associated musculoskeletal deteriorations, such as sarcopenia, osteoporosis, osteoarthritis, and injuries create significant global healthcare burdens. Basic researchers, biomedical engineers, and clinical scientists are now collaborating to develop innovative treatments where the understanding on underlying mechanisms of pathophysiology and injury is the foundation for clinical translation.

Bone metabolic disorders, such as osteoporosis impairs the skeletal homeostasis involving bone resorption and formation. Zhang M et al. reported X-linked inhibitor of apoptosis protein (XIAP)-associated factor 1 (Xaf1) promoted osteoclast apoptosis by antagonizing the XIAP-caspase axis. Their data illustrated an essential role of Xaf1 in the regulation of osteoclastogenesis in both osteoporosis and osteolysis [1]. Jiang Q et al. reported that Zinc finger-containing transcription factor Osterix/Specificity protein-7 (Sp7) was an essential transcription factor for osteoblast differentiation. Their study indicated that Sp7 inhibited the proliferation of immature osteoblasts, induced osteoblast maturation and Col1a1 expression, and was required for osteocytes to acquire several processes for their survival and prevention of cortical porosity [2]. Neuromusculoskeletal interaction is an important clinical issue in aging, but the underlying mechanisms are largely unknown. Lin W et al. conducted a systematic review on Wnt/β-catenin signaling pathway as an important mediator in muscle and bone crosstalk. The analysis showed that Wnt3a, Wnt4 and Wnt10b played an important mediatory role in muscle-bone crosstalk where Wnt4 was mostly found to regulate muscle from the bone side, whilst the role of Wnt10b during muscle ageing was proposed btu current evidence was insufficient to clarify the specific role of Wnt/β-catenin signaling in the interplay between sarcopenia and osteoporosis [3].

Osteonecrosis of femoral head (ONFH) is a challenging skeletal disorder where subchondral fracture line of femoral head occurs most frequently in anterolateral femoral head. Wu Y–B et al. evaluated 3D distribution of subchondral fracture lines in ONFH and explored the underlying mechanisms that contributed to its collapse [4]. Osteomyelitis (OM) is an inflammatory condition of bone characterized by cortical bone devascularization and necrosis. Wei Z et al. identified a new subset IDO1+ CCL3+ CCL4+ osteostaticytes which displayed the highest chemotactic activity among all osteoclast lineages and may serve as reversal cells in bone remodelling. These findings offered new insights and insights for understanding bone reversal-related diseases and might serve as novel therapeutic targets for conditions such as OM and delayed bone healing [5]. Tao X et al. of Professor G Zhang's group reported sclerostin inhibition for osteogenesis imperfecta (OI), a rare bone disease based on molecular understanding for facilitating development of clinical prediction strategies for OI patients responsive to sclerostin inhibition [6].

In osteoarthritis (OA), Kuang SD et al. reviewed how pyroptosis-related crosstalk played a role in OA involving macrophages, fibroblast-like synoviocytes and chondrocytes. The authors comprehensively examined the mechanisms underlying pyroptosis and specifically investigated the intercellular interactions associated with pyroptosis among these three cell types, implying diversity in OA treatment [7]. Fazio A et al. updated the involvement of signaling pathways in OA pathogenesis and highlighted the recent findings on the main pathways involved in OA development, including Wnt, Notch, Hedgehog, MAPK, AMPK, and JAK/STAT that providing insights on current targeted therapies in OA patients' management [8]. Geng N et al. intersected OA dataset GSE82107 from GEO database and senescence dataset from CellAge database of human senescence-associated genes based on genetic manipulations experiments plus gene expression profilin. The hub genes were verified *in vitro* and in human OA cartilage tissues by qRT-PCR. They reported that MAPK12 and FOS could effectively alleviate OA by regulating chondrocyte senescence, and thus provided potential therapeutic targets for exploring prevention or treatment of OA [9]. Liu Y et al. studied the role of sargassum polysaccharide (SP) in attenuating OA in rats and found that was associated with the up-regulation of the ITGβ1-PI3K-AKT signaling pathway, suggesting SP presented compelling scientific evidence for potential advancement of a next-generation polysaccharide drug for OA therapy [10]. Liu R et al. reported that TBK1 pharmacological inhibition mitigated OA through attenuating inflammation and cellular senescence in chondrocytes. Their experimental data suggested BX795 as a promising therapeutic candidate for OA treatment [11]. Numerous approaches have been utilized to optimize mesenchymal stem cells (MSCs) performance in OA treatment. However, the constrained diminished activity and chondrogenic differentiation capacity impeded their therapeutic efficacy. Lin J et al. previously successfully showed that pretreatment with nanosecond pulsed electric fields (nsPEFs) significantly enhanced chondrogenic differentiation of MSCs and in the current study they reported that nsPEFs pretreatment was a simple and effective strategy for improving the MSCs performance and the therapeutic effects for OA treatment [12].

Development of innovative biomaterials is a hot area than need multi-disciplinary efforts towards clinical translation. Luo S et al. conducted a review and highlighted the role of electroactive biomaterials in improving local microenvironment and facilitating bone regeneration. Interactions between osteogenesis-related cells and electroactive biomaterials were also summarized and proposed the use of electrical stimulation-based therapies to accelerate bone healing [13]. Laubach M

https://doi.org/10.1016/j.jot.2024.07.003

Available online 12 July 2024
2214-031X/© 2024 Published by Elsevier B.V. on behalf of Chinese Speaking Orthopaedic Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

et al. reported that biodegradable composite scaffolds loaded with bone grafts from the novel intramedullary harvesting concept and the Reamer-Irrigator-Aspirator 2 (RIA 2) system had equivalent osteogenic capacity, suggested the novel innovative, highly intuitive intramedullary harvesting concept could offer a promising alternative to the RIA 2 system for harvesting bone grafts and its clinical translation [14]. Zhang Z et al. reviewed how copper, an essential trace element for the human body, impacted bone metabolism, especially when copper was sued as an implantable biomaterial for orthopaedic applications where copper ions could be released *in vivo* to affect the function of osteoblasts and osteoclasts, either directly or indirectly by modulating the inflammatory response, oxidative stress, and rapamycin signaling [15]. Li Z et al. reported an interesting and novel concept by combining "waste utilization" and "tissue to tissue" strategies to accelerate vascularization for bone repair. Utilizing autologous tissue grafts from donors offers the dual advantage of mitigating the risk of disease transmission and circumventing the necessity for post-transplant immunosuppression, rendering it an exemplary vascularization strategy. In this study, the authors extracted ad-MVFs from adipose tissue and utilized their strong angiogenic ability to accelerate bone repair by promoting vascularization, thereby realizing a paradigm shift in the utilization of this abundant biological material [16]. Li H et al. reported localized delivery of metformin via 3D printed GelMA-Nanoclay hydrogel scaffold for treatment of diabetic bone defects, with successful loading of the systemic antidiabetic drug metformin onto a hydrogel scaffold for localized delivery. Such unique approach exhibited significant efficacy in mending diabetic bone defects, presenting a promising new avenue for the treatment of such challenging conditions [17].

Anterior cruciate ligament (ACL) revision surgery is common in sports medicine and the choice of artificial ligament to shorten recovery time, thereby enabling patients to return to sport more quickly and effectively, is thought-provoking. Chen T and colleagues of Prof. S Chen's group reported a four-year comparative analysis of return to sport and psychological recovery following ACL revision by comparing artificial ligament with anterior tibial tendon (ATT) allograft in ACL revision surgery. They demonstrated improved joint stability and functionality by using artificial ligaments as compared with allogenic ATT four years after surgery [18]. Bone marrow mesenchymal stem cells (BMSCs) have immense potential in applications for the enhancement of tendon-bone (T-B) healing. Wang L et al. compared the effect of skeletal stem cells (SSCs) with BMSCs on rotator cuff tendon-bone healing and demonstrated the superior therapeutic potential of SSCs over BMSCs in tendon-bone healing [19]. Ma Z et al. used clinical samples for analysis of inflammation in the pathogenesis of chronic tendinopathy and reported that excessive inflammation contributed to the pathogenesis of tendinopathy, where fatty acid binding protein 4 (FABP4) was fund a pro-inflammatory adipokine mediating various metabolic and inflammatory diseases, implying that FABP4 could be a potential treatment target of tendinopathy [20].

In this issue, nerve injury was also reported as a challenging orthopaedic condition as the functional recovery after repair of the peripheral nerve injury remains unsatisfactory. Wang H et al. reported that Fasudil hydrochloride had a remarkable efficacy for improving axon regeneration and remyelination through the ROCK/PI3K/AKT pathway in a transection of sciatic nerve in rat model, implying a translational potential for treating peripheral nerve injury clinically [21].

References

[1] Zhang M, Huang Y, Bai J, Xu W, Shan H, Sheng L, et al. XAF1 promotes osteoclast apoptosis by antagonizing the XIAP-caspase axis. J Orthop Translat 2024 June 7;47:15–28.

[2] Jiang Q, Nagano K, Moriishi T, Komori H, Sakane C, Matsuo Y, et al. Roles of Sp7 in osteoblasts for the proliferation, differentiation, and osteocyte process formation. J Orthop Translat 2024 June 24;47:161–75.

[3] Lin W, Chow SKH, Cui C, Liu C, Wang Q, Chai S, et al. Wnt/β-catenin signaling pathway as an important mediator in muscle and bone crosstalk: a systematic review. J Orthop Translat 2024 June 20;47:63–73.

[4] Wu Y-B, Liu G-B, Li H, Wu J-Z, Tang J-S, Ye J-T, et al. Three-dimensional distribution of subchondral fracture lines in osteonecrosis of the femoral head. J Orthop Translat 2024 June 20;47:97–104.

[5] Wei Z, Zhou J, Shen J, Sun D, Gao T, Liu Q, et al. Osteostaticytes: a novel osteoclast subset couples bone resorption and bone formation. J Orthop Translat 2024 June 20;47:144–60.

[6] Tao X, Wang L, Yang X, Jiang H, Zhang N, Zhang H, et al. Sclerostin inhibition in rare bone diseases: molecular understanding and therapeutic perspectives. J Orthop Translat 2024 June 19;47:39–49.

[7] Kuang S, Sheng W, Meng J, Liu W, Xiao Y, Tang H, et al. Pyroptosis-related crosstalk in osteoarthritis: macrophages, fibroblast-like synoviocytes and chondrocyte. J Orthop Translat 2024 June 29;47:223–34.

[8] Fazio A, Martino AD, Brunello M, Traina F, Marvi MV, Mazzotti A, et al. The involvement of signaling pathways in the pathogenesis of osteoarthritis: an update. J Orthop Translat 2024 June 22;47:116–24.

[9] Geng N, Xian M, Deng L, Kuang B, Pan Y, Liu K, et al. Targeting the senescence-related genes MAPK12 and FOS to alleviate osteoarthritis. J Orthop Translat 2024 June 20;47:50–62.

[10] Liu Y, Lin R, Fang H, Li L, Zhang M, Lu L, et al. Sargassum polysaccharide attenuates osteoarthritis in rats and is associated with the up-regulation of the ITGβ1-PI3K-AKT signaling pathway. J Orthop Translat 2024 June 27;47:176–90.

[11] Liu R, Qu Y, Wang Z, He Z, Xu S, Cheng P, et al. TBK1 pharmacological inhibition mitigates osteoarthritis through attenuating inflammation and cellular senescence in chondrocytes. J Orthop Translat 2024 June 28;47:207–22.

[12] Lin J, Li K, Yang Z, Cao F, Gao L, Ning T, et al. Functionally improved mesenchymal stem cells via nanosecond pulsed electric fields for better treatment of osteoarthritis. J Orthop Translat 2024 July 5;47:235–48.

[13] Luo S, Zhang C, Xiong W, Song Y, Wang Q, Zhang H, et al. Advances in electroactive biomaterials: through the lens of electrical stimulation promoting bone regeneration strategy. J Orthop Translat 2024 June 27;47:191–206.

[14] Laubach M, Herath B, Suresh S, Saifzadeh S, Dargaville BL, Cometta S, et al. An innovative intramedullary bone graft harvesting concept as a fundamental component of scaffold-guided bone regeneration: a preclinical in vivo validation. J Orthop Translat 2024 June 5;47:1–14.

[15] Zhang Z, Tang H, Du T, Yang D. The impact of copper on bone metabolism. J Orthop Translat 2024 June 24;47:125–31.

[16] Li Z, Wang H, Li K, Wang W, Ma J, Liu Z, et al. Combining "waste utilization" and "tissue to tissue" strategies to accelerate vascularization for bone repair. J Orthop Translat 2024 June 24;47:132–43.

[17] Li H, Mao B, Zhong J, Li X, Sang H. Localized delivery of metformin via 3D printed GelMA-Nanoclay hydrogel scaffold for enhanced treatment of diabetic bone defects. J Orthop Translat 2024 July 5;47:249–60.

[18] Chen T, Dong Y, Li Y, Chen S. Four-year comparative analysis of return to sport and psychological recovery following ACL revision: artificial ligament vs. anterior tibial tendon allograft. J Orthop Translat 2024 June 18;47:29–38.

[19] Wang L, Guan C, Zhang T, Zhou Y, Liu Y, Hu J, et al. Comparative effect of skeletal stem cells versus bone marrow mesenchymal stem cells on rotator cuff tendon-bone healing. J Orthop Translat 2024 June 20;47:87–96.

[20] Ma Z, Lee AYW, Kot CH, Yung PSH, Chen S-c, Lui PPY. Upregulation of FABP4 induced inflammation in the pathogenesis of chronic tendinopathy. J Orthop Translat 2024 June 21;47:105–15.

[21] Wang H, Fang F, Jing X, Xu D, Ren Z, Dou S, et al. Augmentation of functional recovery via *ROCK/PI3K/AKT* pathway by Fasudil Hydrochloride in a rat sciatic nerve transection model. J Orthop Translat 2024 June 20;47:74–86.

Ling Qin, Prof

Department of Orthopaedics & Traumatology, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China

E-mail address: lingqin@cuhk.edu.hk.