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# Editorial: The immune system and inflammation in musculoskeletal health, aging, and disease

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## Editorial on the Research Topic

**The immune system and inflammation in musculoskeletal health, aging, and disease**

The musculoskeletal and immune systems are intricately linked in anatomical space and function, with crosstalk between immune cells and musculoskeletal tissues, including bone, cartilage, muscle, and tendons, being essential for normal development and homeostasis (1–4). Such a relationship is also critical during injury and repair, with inflammation and immune cells being necessary for initiating and resolving injury-induced tissue responses and altered extracellular matrix composition and turnover, likewise regulating immune cell engagement (5–9). Over the last decade, growing evidence has demonstrated that alterations to immune cell populations caused by aging and metabolic dysfunction underly the impaired tissue repair responses seen in chronic musculoskeletal diseases and acute injuries, including those affecting synovial joints (e.g., osteoarthritis), bones (e.g., osteoporosis, fracture healing), muscles (e.g., sarcopenia), and tendons/ligaments (e.g., tendinopathy, rupture).

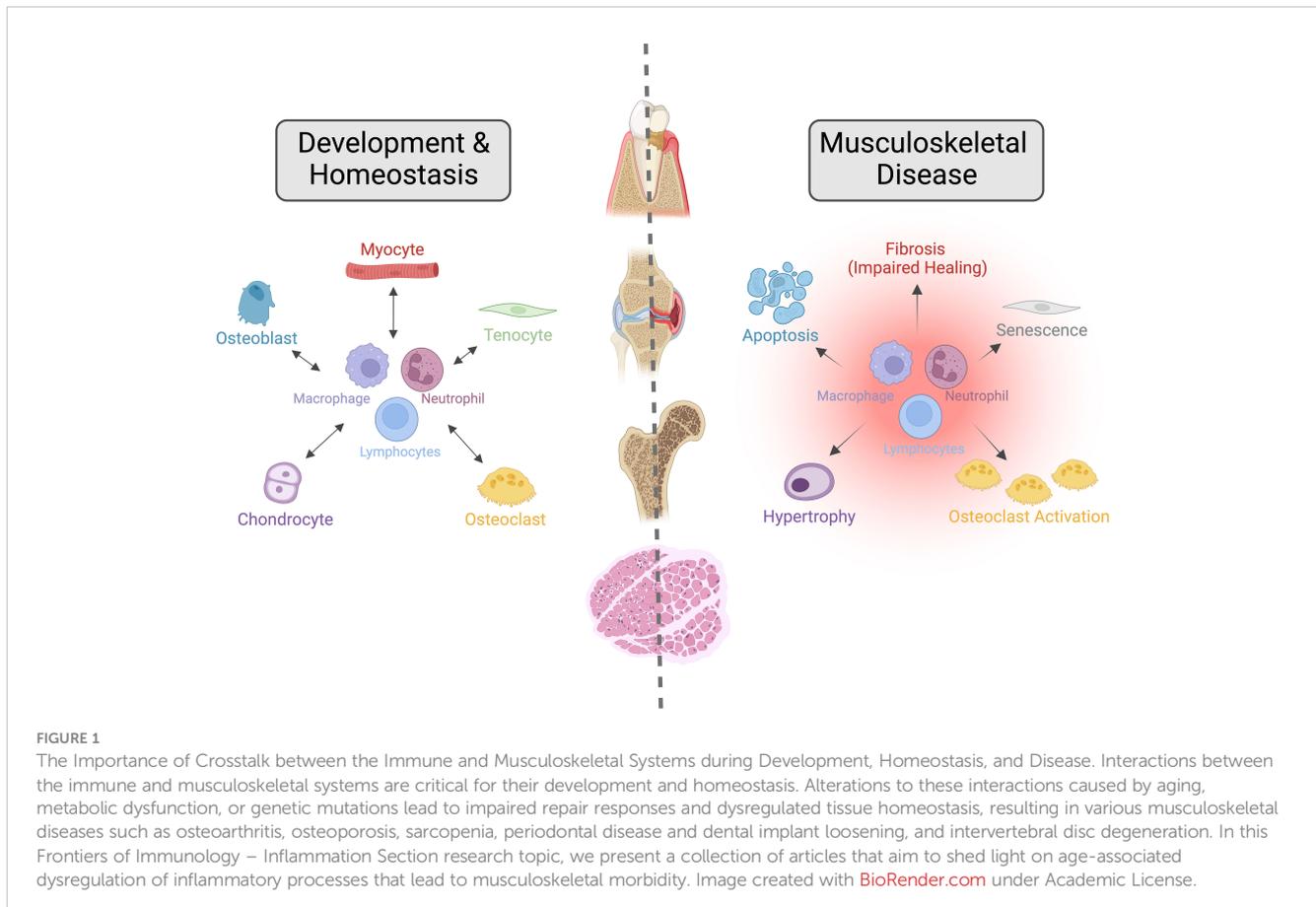
The burden from musculoskeletal conditions continues to rise globally, impacting patients' quality of life, independence, and health, social and economic systems due to increasing care costs and work loss. Over 1.7 billion people globally live with musculoskeletal conditions, according to the World Health Organization (10) and findings from the Lancet's Global Burden of Disease Study 2019 (11–13). Low back pain is the main contributor to this overall burden, while osteoarthritis (OA) shows the most rapid increase of these conditions. While advances have been made in treating osteoporosis in the past decade, intervertebral disc degeneration (IVDD), OA, and many others where disease pathogenesis is less understood lack disease-modifying therapeutics. Progress in understanding how diseases such as IVDD and OA progress has revealed an essential role for inflammatory dysregulation in these conditions; however, several important questions must be resolved before this can be mobilized as a therapeutic strategy. In this Frontiers in Immunology – Inflammation Section Research Topic; The Immune System and Inflammation in Musculoskeletal Health, Aging, and Disease; we present a collection of

articles focused on the aging skeleton and aim to shed light on age-associated dysregulation of inflammatory processes that lead to musculoskeletal morbidity with the hope of identifying targets for future disease-modifying therapeutics (Figure 1).

OA is a multifactorial disease affecting synovial joints and one of the most common musculoskeletal diseases worldwide (14, 15). The disease is characterized by progressive loss of articular cartilage, subchondral bone and peri-articular bone remodeling, and intra-articular inflammation with synovitis, culminating in chronic pain and reduced mobility. The role of immune cells in OA progression was long recognized but remains poorly understood. In this Research Topic, Haubruck et al. outline the role of monocytic cells in post-traumatic OA (PTOA) and discuss therapeutic interventions to potentially improve disease outcomes. In addition to modifying disease outcomes, improved metrics for classifying OA severity are required to better manage the disease and for the development of disease-modifying drugs. In this regard, the search for biomarkers that can identify the stage of OA progression and distinguish between OA at different anatomical sites has become increasingly important. In this Research Topic, Zhang et al. identify extracellular vesicle sub-species that are more prevalent in patients with knee OA and carry a pro-inflammatory cargo, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). In a second study in this Research Topic, Ratneswaran et al. investigated patients with hand OA and identified that circulating cytokines could distinguish OA severity of the trapeziometacarpal joint. Specifically, interleukin-7 (IL-7) was identified as a marker

capable of differentiating disease severity with higher levels associated with a decreased likelihood of trapeziometacarpal joint OA needing surgical intervention. In terms of targeting inflammation to treat OA, Vachhani et al. investigated whether CD200R1 agonists could delay the progression of PTOA; however, neither the protein therapeutic CD200Fc nor the synthetic DNA aptamer CCS13 were able to attenuate cartilage degeneration or synovitis, despite their ability to blunt inflammatory response in the knee. This study points to the complexities of targeting inflammation in complex diseases such as OA.

In recent years, synoviocytes and resident immune cells within the synovium have emerged as key players in the progression of OA and other joint diseases (16, 17). In this Research Topic, Jones et al. used ChIP-seq to assay fibroblast-like synoviocytes and identified that SOX4 and RELA physically interact on chromatin, with TNF-responsive genes being the primary targets of this transcriptional complex. Sodhi et al. identified sex-dependent differences between complement and synovial microvascular pathology in patients, with higher synovial fluid C5 levels being associated with increased complement activation and decreased synovial vascularization in males but not in females with OA. Farina et al. identified that the binding of pro-nerve growth factor to p75NTR on synoviocytes elicits an inflammatory response, resulting in the release of IL-1 $\beta$ , IL-6 and TNF- $\alpha$ . Inhibition of this binding prevented this inflammatory response and represents a novel therapeutic approach in chronic arthritis. Finally, the role of Hippo pathway targets, the mechanoresponsive Yap/Taz transcription factors, was



investigated in the context of rheumatoid arthritis (RA) by Caire et al., where the authors demonstrated that RA activates Yap/Taz within synoviocytes. Treatment with a Yap/Taz inhibitor reversed the RA phenotype indicating their transcriptional inhibition could be relevant to treat inflammatory-related diseases.

Aging also affects other tissues of the skeleton. The effect of oxidative stress on IVDD was studied by Cao et al. Specifically, this group found that *Ccnb1* and *Pkd1* help to regulate oxidative stress during intervertebral disc degeneration and lead to CD8+ T cell infiltration. This work presents *Ccnb1* & *Pkd1* as potential targets for treatment in IVDD. A lesser-considered modality of the aging skeleton is dental health. Schluessel et al. investigated the loosening of dental implants and related gene expression profiles with the loosening of orthopedic implants. Using co-culture systems, disparate and overlapping gene profiles were established, identifying potential therapeutic targets for improving and maintaining the integration of dental and orthopedic implants. Ma et al. investigated the ratio of pro-inflammatory and anti-inflammatory macrophages within the infrapatellar fat pad and subcutaneous fat tissue of patients receiving total knee arthroplasties. The macrophage ratio differed between infrapatellar and subcutaneous fat, with the infrapatellar environment presenting a more inflammatory niche that could be targeted for therapeutic intervention in joint disease.

The works within this collection shed light on the importance of immune cell populations and signaling mechanisms in musculoskeletal disease progression; however, more work is certainly needed before therapeutics targeting these mechanisms can be developed to modify complex diseases such as OA and IVDD.

In conclusion, we thank the contributing authors for sharing their findings and insights in these critical areas. Musculoskeletal diseases have long presented a challenge to the medical and scientific communities. However, with an improved understanding of how the immune and musculoskeletal systems interact, better and more selective therapies could be on the horizon.

## References

- Guder C, Gravius S, Burger C, Wirtz DC, Schildberg FA. Osteoimmunology: a current update of the interplay between bone and the immune system. *Front Immunol* (2020) 11:58. doi: 10.3389/fimmu.2020.00058
- Longoni A, Knezevic L, Schepers K, Weinans H, Rosenberg A, Gawlitta D. The impact of immune response on endochondral bone regeneration. *NPJ Regen Med* (2018) 3:22. doi: 10.1038/s41536-018-0060-5
- Sun Z, Liu B, Luo ZJ. The immune privilege of the intervertebral disc: implications for intervertebral disc degeneration treatment. *Int J Med Sci* (2020) 17:685–92. doi: 10.7150/ijms.42238
- Tidball JG. Regulation of muscle growth and regeneration by the immune system. *Nat Rev Immunol* (2017) 17:165–78. doi: 10.1038/nri.2016.150
- Baht GS, Vi L, Alman BA. The role of the immune cells in fracture healing. *Curr Osteoporos Rep* (2018) 16:138–45. doi: 10.1007/s11914-018-0423-2
- Crosio G, Huang AH. Innate and adaptive immune system cells implicated in tendon healing and disease. *Eur Cell Mater* (2022) 43:39–52. doi: 10.22203/eCM.v043a05
- Woodell-May JE, Sommerfeld SD. Role of inflammation and the immune system in the progression of osteoarthritis. *J Orthop Res* (2020) 38:253–7. doi: 10.1002/jor.24457
- Xiong Y, Mi BB, Lin Z, Hu YQ, Yu L, Zha KK, et al. The role of the immune microenvironment in bone, cartilage, and soft tissue regeneration: from mechanism to therapeutic opportunity. *Mil Med Res* (2022) 9:65. doi: 10.1186/s40779-022-00426-8
- Ye F, Lyu FJ, Wang H, Zheng Z. The involvement of immune system in intervertebral disc herniation and degeneration. *JOR Spine* (2022) 5:e1196. doi: 10.1002/jsp2.1196
- Organization WH. Musculoskeletal health (2022).
- Diseases GBD, Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet* (2020) 396:1204–22. doi: 10.1016/S0140-6736(20)30925-9
- Liu S, Wang B, Fan S, Wang Y, Zhan Y, Ye D. Global burden of musculoskeletal disorders and attributable factors in 204 countries and territories: a secondary analysis of the global burden of disease 2019 study. *BMJ Open* (2022) 12:e062183. doi: 10.1136/bmjopen-2022-062183
- Sebbag E, Felten R, Sagez F, Sibilia J, Devilliers H, Arnaud L. The world-wide burden of musculoskeletal diseases: a systematic analysis of the world health organization burden of diseases database. *Ann Rheum Dis* (2019) 78:844–8. doi: 10.1136/annrheumdis-2019-215142
- Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum* (2012) 64:1697–707. doi: 10.1002/art.34453
- Martel-Pelletier J, Barr AJ, Cicuttini FM, Conaghan PG, Cooper C, Goldring MB, et al. Osteoarthritis. *Nat Rev Dis Primers* (2016) 2:16072. doi: 10.1038/nrdp.2016.72
- Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. *Arthritis Res Ther* (2017) 19:18. doi: 10.1186/s13075-017-1229-9
- Yoshitomi H. Regulation of immune responses and chronic inflammation by fibroblast-like synoviocytes. *Front Immunol* (2019) 10:1395. doi: 10.3389/fimmu.2019.01395

## Author contributions

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