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EDITED AND REVIEWED BY
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SPECIALTY SECTION
This article was submitted to
Autoimmune and Autoinflammatory
Disorders: Autoimmune Disorders,
a section of the journal
Frontiers in Immunology

RECEIVED 04 November 2022
ACCEPTED 10 November 2022
PUBLISHED 21 November 2022

CITATION
Chen Z, Leceta J, Abdul-Sater AA and
Delgado M (2022) Editorial: The innate
immune system in
rheumatoid arthritis.
Front. Immunol. 13:1089522.
doi: 10.3389/fimmu.2022.1089522

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Editorial: The innate immune system in rheumatoid arthritis

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KEYWORDS

arthritis, rheumatoid, innate immunity, inflammation, osteoclast

Editorial on the Research Topic

The innate immune system in rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune-mediated inflammatory disease that affects around 1% of world population. It is the consequence of a failure in self-tolerance mechanisms that facilitate the production of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) (1). Although dysregulated adaptive immune system as a key player in the pathogenesis of RA have been thoroughly investigated, increasing attention is also being paid to the involvement of the innate immune system in RA (2, 3). Cells of the innate immune system, such as monocytes, macrophages, neutrophils, dendritic cells, and innate lymphoid cells (ILCs), have been implicated in the development, chronicity and resolution phase of RA (2, 3). Hence, understanding how the innate immune system participates in the mechanisms of inflammatory processes as well as bone damage of RA is of great importance.

Activation of the NLRP3 inflammasome and subsequent induction of pro-inflammatory cytokines like IL-1 β and IL-18 have been demonstrated in both arthritic animal models and RA patients (4–6). Yin et al. reviewed the current evidence of NLRP3 inflammasome involvement in RA pathogenesis, indicating that inhibition of NLRP3 inflammasome-related signaling pathway could be employed as a potential therapeutic target. Platelets are recognized as innate immune cells and elevated circulating platelet numbers are associated with more severe RA (7). Jiang et al. summarized the latest knowledge on the role of platelet activation in the pathogenesis of RA. Indeed, platelet-based therapeutic targets for RA have been explored (8).

Osteoclasts are the sole bone-resorbing cells that are responsible for the bone erosion in RA. It has been established that Fc γ R signaling promotes osteoclast differentiation and bone loss in RA, whereas interferon (IFN) γ secreted by immune cells blocks osteoclast activation (9, 10). In this Research Topic, Groetsch et al. investigated the interconnection between the two pathways in regulating osteoclast differentiation in RA. Interestingly, they found that the inhibitory effect of IFN γ on human osteoclast differentiation depends on the osteoclast differentiation stage indicating that IFN γ R activation inhibits the formation of osteoclasts in

early osteoclast precursors but is enhanced in premature osteoclasts. Furthermore, IFN γ R activation on early precursor cells, but not on premature osteoclasts, induces Fc γ R expression, suggesting a co-regulation of both receptors on osteoclast differentiation, which might reflect their distinct role in different stages of RA.

Periodontitis (PD) has been linked to the development of RA in previous observational studies (11). Yin et al investigated the causal association of PD with RA by a two-sample bidirectional Mendelian randomization (MR) analysis. Surprisingly, their results reveal non-causal association of PD with RA, suggesting that more mechanistic studies are needed to validate the association of PD with RA.

The aryl hydrocarbon receptor (AHR) signaling pathway has been implicated in the regulation of inflammatory diseases including RA (12). Zhang et al explored the association of single nucleotide polymorphisms (SNPs) of AHR signaling pathway genes with RA susceptibility. Despite the absence of significant association between AHR gene polymorphisms and RA susceptibility, they found altered AHR methylation levels were related to the risk of suffering RA.

Collectively, the original research and mini-review articles in this Research Topic cover a series of important aspects in the field of innate immune system in RA.

References

- Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. *Nat Rev Dis Primers* (2018) 4:18001. doi: 10.1038/nrdp.2018.1
- Edilova MI, Akram A, Abdul-Sater AA. Innate immunity drives pathogenesis of rheumatoid arthritis. *BioMed J* (2021) 44(2):172–82. doi: 10.1016/j.bj.2020.06.010
- Fang W, Zhang Y, Chen Z. Innate lymphoid cells in inflammatory arthritis. *Arthritis Res Ther* (2020) 22(1):25. doi: 10.1186/s13075-020-2115-4
- Guo C, Fu R, Wang S, Huang Y, Li X, Zhou M, et al. NLRP3 inflammasome activation contributes to the pathogenesis of rheumatoid arthritis. *Clin Exp Immunol* (2018) 194(2):231–43. doi: 10.1111/cei.13167
- Jager E, Murthy S, Schmidt C, Hahn M, Strobel S, Peters A, et al. Calcium-sensing receptor-mediated NLRP3 inflammasome response to calciprotein particles drives inflammation in rheumatoid arthritis. *Nat Commun* (2020) 11(1):4243. doi: 10.1038/s41467-020-17749-6
- Dong X, Zheng Z, Lin P, Fu X, Li F, Jiang J, et al. ACPAs promote IL-1 β production in rheumatoid arthritis by activating the NLRP3 inflammasome. *Cell Mol Immunol* (2020) 17(3):261–71. doi: 10.1038/s41423-019-0201-9
- Targonska-Stepniak B, Grzechnik K, Zwolak R. The relationship between platelet indices and ultrasound, clinical, laboratory parameters of disease activity in patients with rheumatoid arthritis. *J Clin Med* (2021) 10(22):5259. doi: 10.3390/jcm10225259
- Cafaro G, Bartoloni E, Alunno A, Gerli R. Platelets: a potential target for rheumatoid arthritis treatment? *Expert Rev Clin Immunol* (2019) 15(1):1–3. doi: 10.1080/1744666X.2019.1544071
- Zuo Y, Deng GM. Fc gamma receptors as regulators of bone destruction in inflammatory arthritis. *Front Immunol* (2021) 12:688201. doi: 10.3389/fimmu.2021.688201
- Tang M, Tian L, Luo G, Yu X. Interferon-Gamma-Mediated osteoimmunology. *Front Immunol* (2018) 9:1508. doi: 10.3389/fimmu.2018.01508
- Gonzalez-Febles J, Rodriguez-Lozano B, Sanchez-Piedra C, Garnier-Rodriguez J, Bustabad S, Hernandez-Gonzalez M, et al. Association between periodontitis and anti-citrullinated protein antibodies in rheumatoid arthritis patients: a cross-sectional study. *Arthritis Res Ther* (2020) 22(1):27. doi: 10.1186/s13075-020-2121-6
- Lahoti TS, John K, Hughes JM, Kusnadi A, Murray IA, Krishnegowda G, et al. Aryl hydrocarbon receptor antagonism mitigates cytokine-mediated inflammatory signalling in primary human fibroblast-like synoviocytes. *Ann Rheum Dis* (2013) 72(10):1708–16. doi: 10.1136/annrheumdis-2012-202639

Author contributions

ZC drafted the editorial, JL, AA-S and MD reviewed and revised the editorial. All authors contributed to the article and approved the submitted version.

Conflict of interest

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