In this paper, Yuntian Zhang and Tzongyi Lee, investigated the immune heterogeneity between systemic lupus erythematosus and rheumatoid arthritis based on multi-omics data analysis.

Authors written an interesting paper, the experimental design, data analysis, and conclusions are appropriate for the study for the most part. However, the manuscript's impact can be further improved by expanding the points below.

Line 34, introduction: In RA and LES (autoimmune diseases in general) the damage is caused by self-reactive, adaptive immune responses caused by a loss of tolerance. Authors are invited to expand this concept by discussing the role of infections in RA and LES. In line with what is suggested could be helpful recent studies performed by Bo M, et al. The researchers showed how the loss of tolerance could be triggered by viral and bacterial infections in genetically predisposed people. They found that IRF5 is a potential target of autoimmune response triggered by EBV and MAP in rheumatoid arthritis patients in comparison with the general population.

Some interesting articles are suggested to the authors that will certainly give more strength to the work enriching the content:

- Bo M, et al. Interferon regulatory factor 5 is a potential target of autoimmune response triggered by Epstein-barr virus and Mycobacterium avium subsp. paratuberculosis in rheumatoid arthritis: investigating a mechanism of molecular mimicry. Clin Exp Rheumatol. 2018 May-Jun;36(3):376-381. Epub 2018 Jan 15.
- Mameli G, et al. Identification of a HERV-K env surface peptide highly recognized in Rheumatoid Arthritis (RA) patients: a cross-sectional case-control study. Clin Exp Immunol. 2017 Jul;189(1):127-131. doi: 10.1111/cei.12964. Epub 2017 May 9.
- Bo M, et al. Antibody response to homologous epitopes of Epstein-Barr virus, Mycobacterium avium subsp. paratuberculosis and IRF5 in patients with different connective tissue diseases and in mouse model of antigen-induced arthritis. J Transl Autoimmun. 2020 Mar 17;3:100048. doi: 10.1016/j.jtauto.2020.100048. eCollection 2020

Line 62: Please explain in more detail the toll-like receptors pathways in RA and LES and the role of TNF in the inflammatory response to bacterial and viral infections taking a cue from the following paper.

- Bo M, et al. Role of Infections in the Pathogenesis of Rheumatoid Arthritis: Focus on Mycobacteria. Microorganisms. 2020 Sep 23;8(10):1459. doi: 10.3390/microorganisms8101459.

Line 45: please explain the importance of IL-2 in the regulation of T cell functions. Anti-inflammatory T regulatory cells (Tregs) are known for their essential role in the conservation of tolerance to self-antigens as well as in the regulatory mechanisms of immune-mediated inflammation. IL-2 is a pleiotropic cytokine indispensable for proper Treg cell function, making it an attractive target in autoimmune disease. Please explain the possible relation between Tregs, loss of immune tolerance to IL-2 in autoimmune diseases and Aryl Hydrocarbon Receptor (AhR).

Here an interesting paper which might help:

- Pérol L, et al. Loss of immune tolerance to IL-2 in type 1 diabetes. Nat Commun. 2016 Oct 6;7:13027. doi: 10.1038/ncomms13027.
- Bo M, et al. Rheumatoid arthritis patient antibodies highly recognize IL-2 in the immune response pathway involving IRF5 and EBV antigens. Sci Rep. 2018 Jan 29;8(1):1789. doi: 10.1038/s41598-018-19957-z.

Kind Regards