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HIGHLIGHT

Synovial joints: The barometer of systemic inflammation

KEY WORDS

Synovium immune environment;
A sentinel unit of macrophages-nociceptor neurons;
Joint inflammation and pain;
Cross-organs immune response

Joint is often regarded as a sensitive indicator of systemic inflammation, capable of responding to various pathological states ranging from local infections to systemic inflammatory diseases. We are all familiar with the phenomenon that the joint pain (arthralgia) caused by joint inflammation (arthritis) usually happens when the body has inflammation in other distant unrelated organs such as lupus[1], psoriasis[2], and bacterial enteric infection[3]. The release of circulating antigen-IgG immune complexes (ICs) to joint through fenestrated endothelium[4] is considered as a mediator of this phenomenon[5,6]. But what is less often appreciated is that this concomitant arthritis of systemic inflammation may be a protective mechanism for joint to avoid attack of ICs.

A study recently published in *Nature Immunology* has revealed the interactions between systemic inflammation and synovium and this work makes significant progress to help us understand the mechanisms of joint inflammation and pain during various inflammatory diseases[7]. Hasegawa et al.[7] dissect anatomical location of synovial $PV1^+$ fenestrated capillaries and subset-specific macrophage−nociceptor cross-talk that forms a blood−joint barrier protecting the synovium from circulating immune challenges (Fig. 1).

The homeostasis of synovium tissue is important for joint bone because it is highly vascular which supplies oxygen, nutrients and some harmful molecules (including ICs) when under systemic inflammation to adjacent avascular articular cartilage[8]. So, Hasegawa et al. first analyzed the endothelial cells from single-cell RNA-sequencing data of mouse synovium. They found $PV1^+$ fenestrated capillaries were high in the mouse synovium of arthritis and were specifically located at the interface of the lining and sublining (L−SL interface) layers. The basal function of PV1 and its role in fenestrated capillaries was to play a role in the passage of proteins, water and other nutrient through the fenestrae, which were previous discussed in other organs[9,10]. Therefore, the joint synovium is always changing substances from the circulating blood through $PV1^+$ fenestrated capillaries to sense systemic diseases. The $PV1^+$ fenestrated capillaries let the circulating stimuli gain access to the healthy synovium of L−SL interface. Next, to identify the detailed immune cells responding to the stimulation of ICs released from $PV1^+$ fenestrated capillaries, Hasegawa et al. finally picked three subsets of macrophages up with distinct transcriptomes and ontogenies in mouse synovium including $LYVE1^+CX_3CR1^+$ macrophages, $MHCII^+CD11c^-$ macrophages, and $MHCII^+CD11c^+$ mononuclear phagocytes (MNPs). Synovium macrophages also have key effect in the pathology of osteoarthritis[11]. The spatial distribution density in the whole synovium of these three macrophages differed from each other but were all in proximity to $PV1^+$ capillaries in the L−SL interface. All three macrophages internalized ICs by FcγRs and meanwhile, increased inhibitory receptor FcγRIIb to prevent potentially damaging responses to circulating ICs. Functionally, the three subtypes of synovial macrophages responded differently to ICs. After ICs challenge, $LYVE1^+CX_3CR1^+$ macrophages secreted neutrophil-recruiting chemokine CXCL1/2 to promote neutrophils infiltrating to L-SL interface of synovium. In $MHCII^+CD11c^+$ MNP, cell adhesion and migration gene sets increased after ICs stimulation. The signals activated by ICs in $MHCII^+CD11c^-$ macrophages were defense response, cell adhesion and migration which shared with some of that in $MHCII^+CD11c^+$ MNPs. Interestingly, $MHCII^+CD11c^-$ macrophages and $MHCII^+CD11c^+$ MNPs formed increased aggregates after ICs challenge and tightly entwined around $PV1^+$ capillaries,

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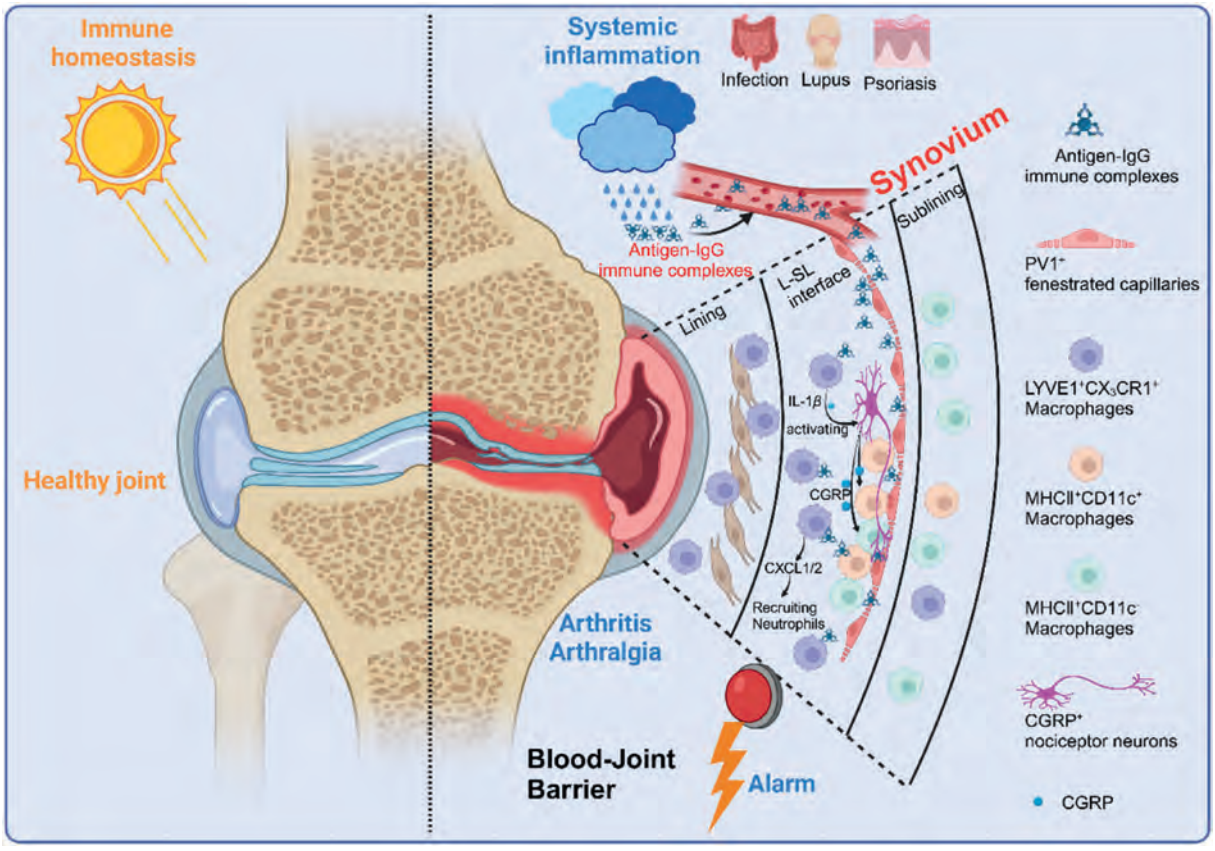

Figure 1 Model of a warning system in synovium when responding to circulating antigen−IgG immune complexes challenges from systemic inflammation. This figure is created with biorender.com.

thus forming a physical barrier that might limit the spread of potentially harmful cargo extravasating from $PV1^+$ capillaries of synovial L−SL interface into the joint.

Hence, Hasegawa et al. found that $PV1^+$ fenestrated capillaries worked as immunological goalkeeper to protect the attack of ICs from blood, which was very different from the traditionally function of vascular architecture in the synovium. And the discovery of these $PV1^+$ fenestrated capillaries as sites of immune complex extravasation opens up new pathways for studying how systemic inflammation influences joint health through impacting synovium health.

Last but not least, Hasegawa et al. found the existence of TH^+ neurons and $CGRP^+$ nociceptor neuronal fibers in the synovium which may process pain. The results indicated that only $CGRP^+$ nociceptor neuronal fibers in the L4 dorsal root ganglia responded indirectly to ICs stimulation through IL-1β released by $LYVE1^+CX_3CR1^+$ macrophages. Moreover, the activated $CGRP^+$ nociceptor neuronal fibers secreted CGRP to activate $MHCII^+$ macrophages and particularly $MHCII^+$ $CD11c^+$ MNPs which became a positive feedforward loop in L−SL interface of synovium to defense system against circulating ICs challenges. Therefore, in this manuscript, neuron−immune interactions enhance host protection from ICs attack through CGRP to modulate innate immune response. The effect of CGRP immunoreactivity from nociceptors on immune cells reported here was partly consistent with previous studies[12,13].

Overall, this paper reveals how a sentinel unit, formed by macrophages and nociceptor neurons in the synovium, collaborate to sense and respond to circulating immune challenges, thereby protecting synovial tissues from inflammatory damage. This discovery not only deepens our understanding of synovial immunology but also offers potential therapeutic targets for treating synovial inflammatory diseases such as rheumatoid arthritis.

Limitations and future work

However, while this study provides an important new insight into the synovial immune defense mechanism, it also has certain limitations and areas for potential improvement. First, lack of discussion on systemic immune effects: Although synovial sentinel units exhibit strong local defensive functions, their impact on the systemic immune system—such as recruiting circulating immune cells or transmitting long-distance signals—has not been thoroughly explored. It remains unclear whether activation of sentinel units might influence systemic immune states, such as triggering systemic inflammation or modulating immune tolerance. Additionally, limited discussion on therapeutic potential and clinical translation: While the paper suggests that sentinel units could be potential targets for treating synovial inflammatory diseases, it does not provide detailed analyses of specific drugs or intervention strategies, such as inhibiting macrophage−neuron interactions. Finally, since the joint pain and inflammation is a warning system, in the present study, there is no evidence to validate that whether synovium inflammation can be targeted and resolved through interrupting macrophage-nociceptor units, which may therefore reduce the reliance of treatment methods for arthritis on broad-acting anti-inflammatory drugs.

In the future, it would be intriguing to investigate whether sentinel units are unique to the synovium or represent a more universal immune mechanism through cross-organ studies (*e.g.*, blood−brain barrier or intestinal barrier). Despite the presence of such a sophisticated sentinel system in the joint synovium, joint pain or inflammation remains common in various systemic pathologies. However, the mechanisms by which these stimuli enter the joint and trigger inflammation are not well understood. Future research elucidating how these stimuli disrupt the blood−joint barrier and lead to joint pain caused by joint inflammation holds significant potential. Additionally, further research on pharmacological interventions to regulate sentinel unit functions and evaluation of their efficacy and side effects in disease models would hold significant clinical relevance. Besides, how to orchestrate the synovial immune environment to regulate $PV1^+$ fenestrated capillaries-neuron-immune crosstalk to regulate inflammation may be imperative in various inflammatory diseases.

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Author contributions

Jie Pan: Writing, review and editing; Original draft writing. Qianqian Liu: Writing, review and editing; Conceptualization. Yang Sun: Review and editing; Funding acquisition and Conceptualization.

Conflicts of interest

The authors declare no competing interests.

References

1. Yan Q, Liu J, Long X, Wu C, Lin D, Wu Y, et al. Tofacitinib therapy in systemic lupus erythematosus with arthritis: a retrospective study. *Clin Rheumatol* 2024;**43**:3139−45.
2. Yu K, Yu X, Cao S, Wang Y, Zhai Y, Yang F, et al. Layered dissolving microneedles as a need-based delivery system to simultaneously alleviate skin and joint lesions in psoriatic arthritis. *Acta Pharm Sin B* 2021;**11**:505−19.
3. Pogreba-Brown K, Austhof E, Tang X, Trejo MJ, Owusu-Dommey A, Boyd K, et al. Enteric pathogens and reactive arthritis: systematic review and meta-analyses of pathogen-associated reactive arthritis. *Foodborne Pathog Dis* 2021;**18**:627−39.
4. Poli A, Mason RM, Levick JR. Effects of Arg−Gly−Asp sequence peptide and hyperosmolarity on the permeability of interstitial matrix and fenestrated endothelium in joints. *Microcirculation* 2004;**11**: 463−76.
5. Waterman HR, Dufort MJ, Posso SE, Ni M, Li LZ, Zhu C, et al. Lupus IgA1 autoantibodies synergize with IgG to enhance plasmacytoid dendritic cell responses to RNA-containing immune complexes. *Sci Transl Med* 2024;**16**:eadl3848.
6. Wu Y, Deshpande A, Geraci N, Budde P, Sellers V, Velisetty P, et al. TLR7/8 activation in immune cells and muscle by RNA-containing immune complexes: role in inflammation and the pathogenesis of myositis. *Arthritis Rheumatol* 2025;**77**:190−201.
7. Hasegawa T, Lee CYC, Hotchen AJ, Fleming A, Singh R, Suzuki K, et al. Macrophages and nociceptor neurons form a sentinel unit around fenestrated capillaries to defend the synovium from circulating immune challenge. *Nat Immunol* 2024;**25**:2270−83.
8. Wei K, Korsunsky I, Marshall JL, Gao A, Watts GFM, Major T, et al. Notch signalling drives synovial fibroblast identity and arthritis pathology. *Nature* 2020;**582**:259−64.
9. Gordon L, Blechman J, Shimoni E, Gur D, Anand-Apte B, Levkowitz G. The fenestrae-associated protein Plvap regulates the rate of blood-borne protein passage into the hypophysis. *Development* 2019;**146**:dev177790.
10. Stan RV, Tse D, Deharvengt SJ, Smits NC, Xu Y, Luciano MR, et al. The diaphragms of fenestrated endothelia: gatekeepers of vascular permeability and blood composition. *Dev Cell* 2012;**23**:1203−18.
11. Sun Z, Liu Q, Lv Z, Li J, Xu X, Sun H, et al. Targeting macrophagic SHP2 for ameliorating osteoarthritis *via* TLR signaling. *Acta Pharm Sin B* 2022;**12**:3073−84.
12. Lu YZ, Nayer B, Singh SK, Alshoubaki YK, Yuan E, Park AJ, et al. CGRP sensory neurons promote tissue healing *via* neutrophils and macrophages. *Nature* 2024;**628**:604−11.
13. Balood M, Ahmadi M, Eichwald T, Ahmadi A, Majdoubi A, Roversi K, et al. Nociceptor neurons affect cancer immunosurveillance. *Nature* 2022;**611**:405−12.

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