



Novel Subset-specific Functions of Dendritic Cells: From Spatiotemporal Regulation of Lymph Node Immunity to Precision Targeting Strategies*

——A Commentary on The Study by Huang & Gerner (*Cell*, 2026)

YANG Shao-Jun, ZHANG Xu-Yuan**

(China State Key Laboratory of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China)

Abstract Dendritic cells (DCs) serve as a crucial link between innate and adaptive immunity and represent key modulatory nodes in the initiation of adaptive immune responses. Although DC-targeted vaccines and therapeutic strategies show great promise, their development remains in the early stages due to a limited understanding of the regulatory mechanisms governing distinct DC subsets in response to various immunogens and types of immune responses. Recently, a study by Jessica Y. Huang and Michael Y. Gerner published in *Cell* has uncovered a novel functional dimension of DCs. Beyond their classical roles in antigen presentation and T cell priming, DCs dynamically regulate the spatiotemporal organization of innate and adaptive immune responses within lymph nodes. During early type I immune responses, tissue-resident DC2s recruit innate immune cells and promote their trafficking, effectively limiting pathogen spread; however, this comes at the cost of disrupting lymph node architecture and suppressing the initiation of adaptive immunity. Following effective pathogen restraint, DCs shift their role to mediate the removal of apoptotic neutrophils and facilitate the restoration of lymph node structure, thereby reinstating adaptive immunity. These findings suggest that a deeper understanding of subset-specific regulatory networks of DCs in various immune contexts may enhance the precision and efficacy of DC-targeted immunotherapies.

Key words dendritic cells, innate immune response, adaptive immune response, DC-targeted immunotherapies

DOI: 10.3724/j.pibb.2026.0177

CSTR: 32369.14.pibb.20260177

Dendritic cells (DCs) have long been recognized as sentinels that bridge innate and adaptive immunity, utilizing their professional antigen-presenting capabilities to orchestrate appropriate immune responses^[1]. They achieve this either through resident dendritic cells sampling draining antigens or by migratory dendritic cells transporting antigens from peripheral tissues to elicit T cell responses primarily in the lymph nodes (LN), which serve as the main sites for immune responses^[2-3].

Before the onset of the adaptive response, various innate effector cells, such as neutrophils, monocytes and natural killer (NK) cells, are recruited to the lymph nodes within hours, where they play critical roles in limiting pathogen dissemination^[4-5]. However, while this recruitment is essential for pathogen control, it can also disrupt the architecture of the lymph nodes, an intact structure that is crucial for initiating adaptive immunity^[6-9]. This raises a

fundamental question: what mechanisms govern the coordination between innate and adaptive responses within the lymph nodes? A recent study by Jessica Y. Huang and Michael Y. Gerner, published in *Cell*, unveils a novel role for dendritic cells as conductors of immune responses^[10]. The study found that DCs regulate the recruitment and organization of innate immune cells within lymph nodes during the early stages of inflammation, thereby restricting pathogen spread. Subsequently, DCs orchestrate the remodeling of lymph node architecture to facilitate the initiation of adaptive immunity. These findings underscore the

* This work was supported by a grant from The National Natural Science Foundation of China (82371853).

** Corresponding author.

Tel: 86-10-64862568, E-mail: zxy_better@ibp.ac.cn

Received: April 7, 2026 Accepted: May 25, 2026

capacity of DCs to exert spatiotemporal control over both cellular composition and immune function within the lymph node.

1 DCs regulate innate cell entry and trafficking

Using spatial correlation analysis and DC depletion model, the authors demonstrate that, in the early stage of type I inflammation, DCs facilitate the efficient entry and migration of innate cells across the lymph parenchyma. They further elucidate the underlying mechanisms. During inflammation, activated resident DCs migrate away from the lymphatic sinuses toward the T-zone, accompanied by the upregulation of numerous inflammatory chemokines. These findings strongly indicate that the haptotactic matrix generated by migrating DCs mediates the recruitment and spatial distribution of innate immune cells. Simultaneously, these cells rapidly increase the expression of the integrin ligand intercellular adhesion molecule 1 (ICAM-1). Through the coordinated provision of a chemokine gradient

and the formation of an adhesion molecule-rich matrix, DCs establish a permissive microenvironment that enhances the trafficking of innate cells. However, the precise mechanism by which DC subsets upregulate ICAM-1 to facilitate the recruitment of innate immune cells remains to be fully elucidated. It would also be of interest to explore whether type I interferon—a pivotal cytokine in type I inflammatory—plays a role in regulating this process.

2 Role of different DCs in innate immune cell trafficking

Consistent with observations that resident type 2 dendritic cell (DC2) primarily localizes near lymphatic sinuses in the steady state and upregulates C-C chemokine receptor type 7 (CCR7) to migrate toward T cell zones upon activation, this study demonstrates that resident DC2 predominantly mediates the recruitment and polarization of innate immune cells (Figure 1). In contrast, resident DC1, which are primarily located around blood vessels, cannot facilitate or may inhibit the trafficking of

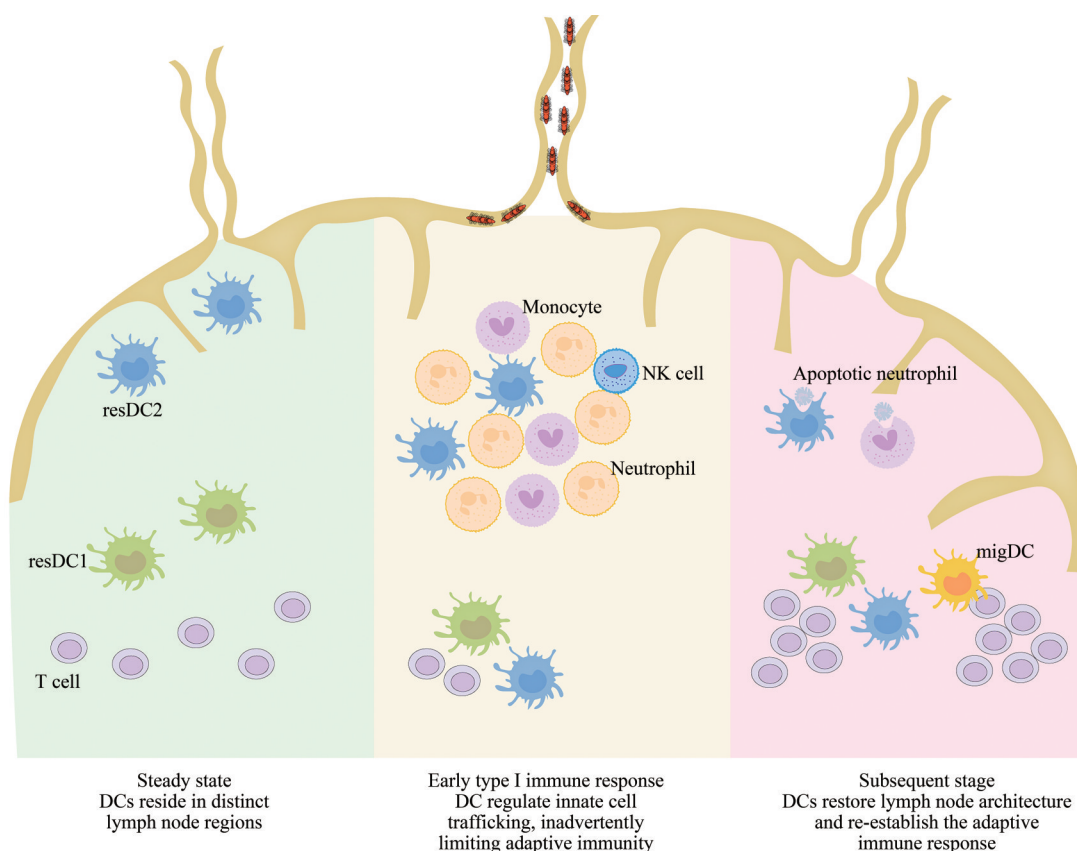


Fig. 1 DCs dynamically regulate the spatiotemporal organization of innate and adaptive immune responses within lymph nodes

resDC1: resident type 1 dendritic cell; resDC2: resident type 2 dendritic cells; migDC: migratory dendritic cell; NK cell: natural killer cell.

innate immune cells. Furthermore, due to their delayed arrival in draining lymph nodes, migratory DCs play a minimal role in modulating the trafficking of innate immune cells. Further clarification may also be beneficial regarding whether resident DC2 directly interact with the recruited innate immune cells.

3 Dual roles of DCs in disrupting and restoring LN architecture

Lymph nodes have two core functions: filtering lymph and mediating immune defense. Innate immunity responds rapidly, typically within hours post-infection, and is primarily localized to the peripheral regions of lymph nodes, thereby preventing the systemic spread of pathogens. In contrast, adaptive immune responses are slower, with detectable responses emerging 3 to 7 d post-infection, and T cell activation mainly occurs in the inner T cell zone^[11].

This paper demonstrates that innate immune cells involved in early-stage infection not only localize to the periphery but also infiltrate the T cell zone and B cell follicles, potentially hindering adaptive immunity^[6-9]. Moreover, following effective pathogen containment, the accumulation of dead neutrophils, if not removed, may cause persistent inflammation. In this context, the authors make a pivotal discovery: DCs are not only involved in initiating immunity but also help clear apoptotic neutrophils and restore lymph node architecture. Using imaging and flow cytometry, they show that at later time points, apoptotic neutrophils were phagocytosed by DCs and DC-recruited monocytes (Figure 1). As neutrophils were cleared, the T cell zone and B cell follicles were restored, with DCs and monocytes localizing to distinct regions within the lymph node, thereby contributing to the shaping of adaptive immunity. Notably, which specific DC subsets perform these distinct functions remains an open question, warranting further investigation.

4 Conclusion and perspectives

In conclusion, this study reveals that DCs not only perform their classic functions of antigen presentation and T cell priming but also regulate the spatiotemporal distribution of both innate and adaptive immune responses within lymph nodes, thereby enabling more effective control of pathogen

spread. However, this regulation can disrupt lymph node architecture and suppress the initiation of adaptive immunity. Previous reports have indicated that vaccine adjuvants such as MF59, an oil-in-water emulsion adjuvant, induce rapid recruitment and transport of neutrophils to draining lymph nodes, however, the trafficking of innate cells does not enhance immune efficiency^[12]. These findings suggest that, in vaccination contexts—where the risk of pathogen dissemination is minimal—fine-tuning DC-mediated innate cell infiltration by optimizing immunization routes, immunogen types, or adjuvants may improve adaptive immune responses.

To achieve this, several targeted strategies can be considered. First, transiently depleting or reprogramming neutrophil subsets may reduce the consumption and degradation of antigens by neutrophils. Second, to avoid excessive innate interference, antigen delivery should be directed specifically to certain DC subsets. Adjuvants that induce type I inflammation, such as the Toll-like receptor 9 (TLR9) agonist cytosine-phosphate-guanine (CpG), can promote the infiltration of innate immune cells into draining lymph nodes, which in turn may hinder adaptive immunity^[10, 13]. Type I interferon, a key cytokine in type I inflammation, has been shown to impair vaccine protection at early stages, its temporary blockade can improve vaccine outcomes^[14]. Therefore, a more refined approach is to use DC subset-targeted vaccines conjugated with adjuvants, ensuring that only antigen-uptaking cells receive activation signals. This strategy minimizes the broad innate activation caused by adjuvant diffusion. Ideally, a targeting strategy that enables effective vaccine immunity without the need for adjuvants would represent a particularly attractive approach.

Looking ahead, further investigation is required to decipher the distinct contributions and modulatory landscapes of various DC subsets in response to different immunogens or types of immune responses. Such efforts will improve the resolution of vaccine-induced immune responses and lay the groundwork for more precise DC-targeted therapies.

References

- [1] Cabeza-Cabrerizo M, Cardoso A, Minutti C M, *et al.* Dendritic cells revisited. *Annu Rev Immunol*, 2021, **39**: 131-166
- [2] Huang JY, Lyons-Cohen MR, Gerner MY. Information flow in the spatiotemporal organization of immune responses. *Immunol Rev*,

- 2022, **306**(1): 93-107
- [3] Huang J Y, Gerner M Y. Dendritic cell organization and function in innate and adaptive immune defense within lymph nodes. *Immunol Rev*, 2026, **337**(1): e70071
- [4] Kastenmüller W, Torabi-Parizi P, Subramanian N, *et al.* Aspatially-organized multicellular innate immune response in lymph nodes limits systemic pathogen spread. *Cell*, 2012, **150**(6): 1235-1248
- [5] Kienle K, Glaser K M, Eickhoff S, *et al.* Neutrophils self-limit swarming to contain bacterial growth *in vivo*. *Science*, 2021, **372**(6548): eabe7729
- [6] Fonseca D M, Hand T W, Han S J, *et al.* Microbiota-dependent sequelae of acute infection compromise tissue-specific immunity. *Cell*, 2015, **163**(2): 354-366
- [7] McCarthy M K, Reynoso G V, Winkler E S, *et al.* MyD88-dependent influx of monocytes and neutrophils impairs lymph node B cell responses to chikungunya virus infection *via* Irf5, Nos2 and Nox2. *PLoS Pathog*, 2020, **16**(1): e1008292
- [8] Kamenyeva O, Boularan C, Kabat J, *et al.* Neutrophil recruitment to lymph nodes limits local humoral response to *Staphylococcus aureus*. *PLoS Pathog*, 2015, **11**(4): e1004827
- [9] Sammiceli S, Kuka M, di Lucia P, *et al.* Inflammatory monocytes hinder antiviral B cell responses. *Sci Immunol*, 2016, **1**(4): eaah6789
- [10] Huang J Y, Gerner M Y. Dendritic cells regulate the innate-adaptive balance in lymph nodes for optimal host defense. *Cell*, 2026, **189**(2): 548-568.e19
- [11] Qi H, Kastenmüller W, Germain R N. Spatiotemporal basis of innate and adaptive immunity in secondary lymphoid tissue. *Annu Rev Cell Dev Biol*, 2014, **30**: 141-167
- [12] Calabro S, Tortoli M, Baudner B C, *et al.* Vaccine adjuvants alum and MF59 induce rapid recruitment of neutrophils and monocytes that participate in antigen transport to draining lymph nodes. *Vaccine*, 2011, **29**(9): 1812-1823
- [13] Leal J M, Huang J Y, Kohli K, *et al.* Innate cell microenvironments in lymph nodes shape the generation of T cell responses during type I inflammation. *Sci Immunol*, 2021, **6**(56): eabb9435
- [14] Broomfield B J, Tan C W, Qin R Z, *et al.* Transient inhibition of type I interferon enhances CD8⁺ T cell stemness and vaccine protection. *J Exp Med*, 2025, **222**(5): e20241148

DC亚群特异性新功能：从淋巴结免疫时空调控到精准靶向策略展望*

——基于Huang & Gerner发表于《细胞》的研究的评述

杨少君 张旭媛**

(中国科学院生物物理研究所生物大分子全国重点实验室, 北京 100101)

摘要 树突状细胞(DCs)作为连接天然免疫与适应性免疫的桥梁,在启动和调节适应性免疫应答中发挥关键作用。尽管靶向DCs的疫苗与治疗策略具有广阔前景,但受限于对不同DCs亚群在各类免疫原及免疫应答类型中的调控机制认知不足,该领域仍处于早期探索阶段。近期, Jessica Y. Huang与Michael Y. Gerner在《细胞》(*Cell*)杂志发表的研究揭示了DCs的新功能:除了经典的抗原提呈与T细胞激活作用外,DCs还能动态调控淋巴结内天然与适应性免疫应答的时空分布。研究发现,在I型免疫应答早期,组织驻留的DC2通过募集天然免疫细胞并促进其定向迁移,能够有效抑制病原体扩散,但这一过程会破坏淋巴结结构并抑制适应性免疫的启动。当病原体被控制后,DC转而介导凋亡中性粒细胞的清除和淋巴结结构的重建,从而恢复适应性免疫应答。这一发现表明,深入解析DCs在不同免疫情境中的亚群特异性调控网络,将有助于提高靶向DCs免疫干预的精准性与分辨率。

关键词 树突状细胞, 天然免疫应答, 适应性免疫应答, DC靶向治疗

中图分类号 R392, Q939.91

DOI: 10.3724/j.pibb.2026.0177

CSTR: 32369.14.pibb.20260177

* 国家自然科学基金(82371853)资助项目。

** 通讯联系人。

Tel: 010-64862568, E-mail: zxy_better@ibp.ac.cn

收稿日期: 2026-04-07, 接受日期: 2026-05-25