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EDITORIAL

Dendritic cells in focus: mapping functional diversity through technological innovation

Francesco Andreata[1,2], Francesca Granucci[3] and Laura Marongiu[3]

1 Division of Immunology, Transplantation and Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy
2 Vita–Salute San Raffaele University, Milan, Italy
3 Department of Biotechnology and Biosciences, University of Milano-Bicocca, Milan, Italy

Since their initial identification by Ralph Steinman and Zanvil Cohn in the 1970s [1], dendritic cells (DCs) have been established as critical regulators of immune responses. While initially characterized as a relatively homogeneous population of potent antigen-presenting cells responsible for priming naïve T lymphocytes, it is now recognized that DCs comprise a complex and heterogeneous network of subsets. These include conventional DCs (cDC1 and cDC2), plasmacytoid DCs (pDCs), and monocyte-derived inflammatory DCs, each exhibiting distinct developmental origins, surface marker expression, and specialized functional

Francesco Andreata is an Assistant Professor of Applied Biology at Vita-Salute San Raffaele University. His research explores how the liver microenvironment shapes CD8 T-cell dysfunction during chronic infections and cancer, with a focus on developing targeted immunotherapies. He has received the *MERU Foundation Career Development Award*, a Starting Grant from the *Italian Science Fund* (*FIS*), and the *Antonio Feltrinelli Prize for Biology* (under 40) from the *Accademia Nazionale dei Lincei*.

Francesca Granucci is Full Professor of General Pathology at the Department of Biotechnology and Biosciences, University of Milano-Bicocca. She leads a research group focused on innate immunity, with particular emphasis on dendritic cell biology. Her work has significantly advanced the understanding of host–pathogen interactions, elucidating the roles of CD14 and the NFAT signaling pathway in regulating immune responses to bacterial and fungal infections. Her scientific contributions have been recognized with several awards, including the *EFIS-EJI Ita Askonas Award* in 2012 and the *IUBMB Jubilee Medal* in 2019.

Laura Marongiu is an Assistant Professor of General Pathology at the Department of Biotechnology and Biosciences, University of Milano-Bicocca. Her research is focused on the molecular regulation of immune responses and stem cell biology, with particular emphasis on the CaN-NFAT signaling pathway. Her current studies investigate the therapeutic potential of modulating calcineurin signaling to promote endogenous stem cell expansion and tissue regeneration. She has been awarded competitive research funding from the *Italian Multiple Sclerosis Association* (*AISM*) and from the *Italian Ministry of University and Research* (*MIUR*) through a *PRIN grant*, and has received the *Young Talents Award* from the University of Milano-Bicocca.

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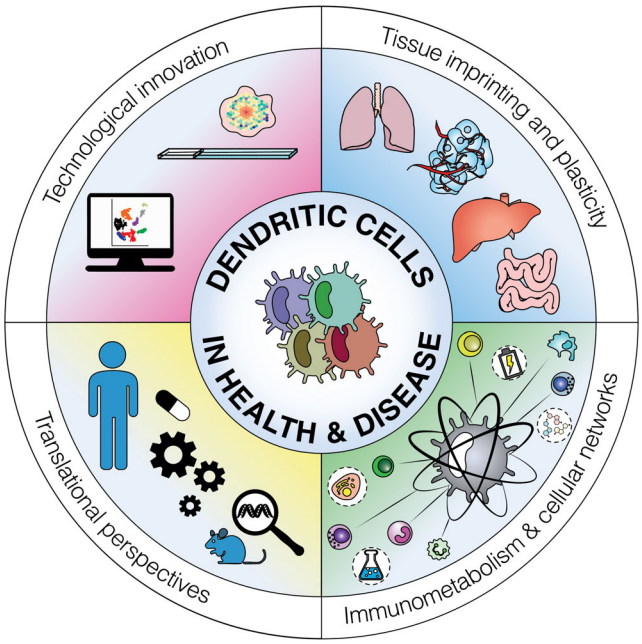

Fig. 1. Key themes of this Special Issue. At the center, a dendritic cell (DC) symbolizes the field's conceptual focus. Surrounding quadrants represent the field's research topics: technological innovations, highlighting tools, such as single-cell RNA sequencing and spatial transcriptomics; tissue imprinting and plasticity, with local microenvironments shaping DC identity; immunometabolism and cellular networks, emphasizing the integration of metabolic and signaling cues; and translational perspectives, linking DC biology to clinical applications. Together, these axes illustrate how the convergence of advanced technologies and tissue context is reshaping the landscape of dendritic cell research.

properties. The phenotypic and functional characteristics of DCs are significantly influenced by the tissue microenvironment in which they reside, with DCs in the skin, lung, intestine, lymph nodes, and tumors demonstrating context-specific programs. This remarkable plasticity underscores the role of DCs not only as initiators of immunity but also as dynamic modulators of immune homeostasis, tolerance, and inflammation.

The *FEBS Letters* Special Issue 'Dendritic cells in health and disease' focuses on recent conceptual and technological advancements that are refining our understanding of DC biology (Fig. 1). The included articles investigate DCs across diverse tissues and disease states, highlighting the translation of technological innovation into novel therapeutic perspectives.

A fundamental aspect of understanding DC identity lies in recognizing that context is a critical determinant of their properties. Whether located within a lymph node or residing in the lung, DCs exhibit adaptability in their morphology, function, and fate. The coordinated action of resident and migratory DCs in lymph nodes, a topic further explored in this issue, illustrates the influence of the spatial and temporal dynamics of immune cell interactions on T-cell activation.

Expanding beyond tissue architecture, the liver provides a relevant example of the intricate relationship between metabolic cues and immune regulation, positioning immunometabolism as a central aspect of DC biology. In their Review, Klaimi *et al.* [2] examine hepatic DCs as integrators of dietary, microbial, and metabolic signals. Their work elucidates how these cells modulate their functions to promote either immune tolerance or inflammation in metabolic dysfunction-associated steatotic liver disease (MASLD). By integrating data from animal models and human pathology, they emphasize the liver as a key site of convergence between immune and metabolic regulation, with DCs occupying a pivotal position at this interface.

To further delineate the evolving understanding of DC heterogeneity, this Special Issue features a series of Reviews providing both mechanistic insights and methodological guidance. In their Review, Protti and Spreafico offer a comprehensive guide to the application of single-cell RNA sequencing (scRNA-seq) in DC research [3]. Their article details the technical and computational workflow, demonstrating the utility of scRNA-seq in the high-resolution dissection of DC subsets and their ontogeny. Importantly, they

also outline strategies for the integration of transcriptomic data with surface marker analysis and functional assays, providing a framework for the classification and comparison of DC populations across various conditions.

Building on the theme of cellular diversity, Nelli and Kuka introduce the concept of TDCs, a novel population co-expressing dendritic and T-cell markers. Their 'In a Nutshell' article explores the ontogeny, molecular profile, and potential immunological functions of these cells, challenging conventional lineage definitions and calling for a re-evaluation of immune cell classification [4]. The identification of TDCs highlights the importance of high-dimensional analytical tools and flexible conceptual frameworks for the identification of rare or transitional populations within the immune system.

The application of spatial biology is increasingly essential for a comprehensive understanding of cellular behavior, incorporating not only molecular identity but also the spatial context of cellular interactions. This approach complements traditional transcriptomic and phenotypic analyses by providing information regarding cellular localization and interaction networks. In the context of DCs, their spatial positioning within tissues, their interactions with neighboring cells, and their migratory patterns are proving to be significant determinants of their function. Reflecting this trend, Rocca *et al.* [5] explore current spatial technologies in their 'In a Nutshell' article. Multiplex immunofluorescence and spatial transcriptomics enable the mapping of DCs within their native environments and reveal how tissue structure and cellular neighborhoods influence DC function, particularly in complex environments, such as tumors and mucosal surfaces.

From a translational perspective, Morali *et al.* [6] provide an in-depth overview of IL-10-producing tolerogenic DCs (tolDCs) as potential cellular therapies for autoimmunity and transplantation. Their Review discusses the molecular mechanisms underlying tolDC function, the challenges associated with maintaining phenotypic stability, and the current limitations in clinical translation. Complementing these mechanistic and therapeutic perspectives, Dotta *et al.* [7] examine the dynamic regulation of antigen and leukocyte trafficking by DCs within lymph nodes. Their 'In a Nutshell' article highlights the interplay between resident and migratory DCs, the role of spatial compartmentalization, and the temporal aspects of activation signals in shaping the efficiency and quality of T-cell priming.

Reflecting on the intersection between subset diversity and translational relevance, Barcelos *et al.* [8] examine how DCs are dynamically reprogrammed within the tumor microenvironment and evaluate strategies to restore or harness their function for cancer immunotherapy. Their Review offers a detailed analysis of DC subset ontogeny, highlights the influence of immunosuppressive signals on DC plasticity, and discusses therapeutic avenues, including mRNA vaccines, CD40 agonists, and *in situ* cellular reprogramming. Emphasizing insights from spatial and single-cell technologies, they propose a framework for designing context-aware, subset-specific interventions to overcome tumor-induced immune dysfunction.

The contributions within this Special Issue underscore the multifaceted nature of DC biology. Encompassing single-cell and spatial technologies, the identification of novel cell types, and the development of therapeutic strategies, these articles collectively illustrate a field in the midst of important breakthroughs. The convergence of technological innovation, functional analysis, and clinical insights is redefining our approach to studying and manipulating DCs. Continued interdisciplinary collaboration will be crucial in realizing the full diagnostic and therapeutic potential of DCs.

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Correspondence
F. Andreata, Division of Immunology, Transplantation and Infectious Diseases, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy
Tel: +39 0226 438144
E-mail: andreata.francesco@hsr.it
and
F. Granucci and L. Marongiu, Department of Biotechnology and Biosciences, Piazza della Scienza, 20126 Milano Italy
Tel: +39 0264 483553, +39 0264 483423
E-mail: francesca.granucci@unimib.it, laura.marongiu@unimib.it