Immune cell states: critical building blocks of the plant immune system

Tatsuya Nobori*

The Sainsbury Laboratory, University of East Anglia, Norwich Research Park, Norwich, United Kingdom

*Correspondence: tatsuya.nobori@tsl.ac.uk

Plant immunity emerges as cells, normally dedicated to non-immune functions, transition their states through diverse mechanisms to engage in defense roles. This Forum explores the concept of plant immune cell states, their biological significance, and emerging approaches to study them, highlighting the complex cellular basis of plant-microbe interactions.

Multicellularity in the plant immune system

Our understanding of plant immunity has advanced significantly over the past 50 years–from molecular identification and biochemical characterization of resistance genes to reconstructing complex molecular networks (Jones et al. 2024). While plants and animals share some similarities in their innate immune systems, including the nature of non-self recognition and signaling molecules, fundamental cellular differences set them apart. Animals employ specialized and mobile immune cells, such as monocytes, neutrophils, and natural killer cells, which circulate through the body to detect and eliminate pathogens. In stark contrast, plants lack dedicated immune cell types. Individual plant cells, which are generally immobile, must be immunocompetent and coordinate with each other to protect the tissue from unpredictable pathogen attacks. Recent advances in genomics and cell biology approaches have revealed that pathogen-infected plant tissues comprise various kinds of cells with distinct molecular profiles. This emerging paradigm necessitates a re-examination of our gene- (or gene product-) centric view of plant immunity to incorporate a cell-centric perspective. How can plant cells be categorised into meaningful functional units beyond developmental cell types to better comprehend the complexity of the immune system? Understanding immune cell state diversity, function, regulation, and interactions is crucial for unravelling the complex multicellularity of the plant immune system.

What are cell states in plants?

The distinction between cell types and states remains debated, with no universal consensus. Cells continuously change their molecular profiles as they progress through the cell cycle and respond to

Accepted manuscript version of:
Nobori T., “Immune cell states: critical building blocks of the plant immune system” *Cell Host & Microbe*, 2025. DOI: https://doi.org/10.1016/j.chom.2025.06.016

various signals (Rusnak et al. 2024). While new cell types typically emerge through cell division, boundaries between cell types and states often blur due to continuous cellular transitions. Here, I define a "cell state" as a variation of a “cell type”–a recurring developmental pattern with distinctive molecular and/or cell biological features–influenced by internal and external factors. In plants, where no dedicated immune cell types have been identified, any cell that activates immune responses is regarded as entering an immune state–a functional state of an existing cell type.

Cell state classification cannot rely solely on molecular profiles. Plant cells from different developmental lineages (e.g., mesophyll and epidermis) may display nearly identical molecular signatures during immune activation, overriding their cell type molecular identity. Despite this molecular similarity, it would be more informative to consider these cells as distinct cell states because they originate from different developmental cell types with distinct lineages and spatial locations. These cells can also diverge in their response at later time points, as immune responses are dynamic processes. Thus, robust cell state definition requires integrating current molecular and positional information with cellular history, such as developmental trajectories and past exposure to environmental stimuli.

Ultimately, no two cells are identical at the molecular and spatiotemporal level. While individual plant cells may be unambiguously defined in some cases (e.g., early embryogenesis), categorizing cells remains essential for studying basic units of multicellular organisms with current experimental and computational tools. Thus, a cell state can be pragmatically defined as a group of cells within a cell type sharing reproducible molecular and positional features and cellular history. This classification is inherently flexible, shaped by both research questions and available technologies.

What shapes plant immune cell states?

Here I will discuss three factors that influence immune cell states (Figure 1A).

(1) Pre-existing immune potential

Even before the pathogen challenge, plant cells possess varying capacities to mount immune responses—their pre-existing immune potential. This potential might be primarily shaped by developmental cell types, which have specific wiring of molecular pathways, including specific expression of immune receptors, to conduct specific functions. Cell type-specific plant responses to pathogens have been shown through imaging and cell type-enriched omics analyses (Fröschel and Dröge-Laser 2023). Cell type-specific immune potential can also be influenced by abiotic factors (e.g., temperature and nutrient availability) and internal cues (e.g., cell cycle phases). Thus, a plant cell's immune state reflects both its developmental trajectory and its history of environmental inputs. The

Accepted manuscript version of:
Nobori T., “Immune cell states: critical building blocks of the plant immune system” *Cell Host & Microbe*, 2025. DOI: https://doi.org/10.1016/j.chom.2025.06.016

field has fragmented knowledge about the diversity of pre-existing immune potentials and their underlying mechanisms.

(2) (Non-)Cell-autonomous immune responses

Pathogen infection creates two fundamentally different situations in plant cells: cells directly exposed to pathogens (including physical interactions with pathogen cells and direct sensing of pathogen-derived molecules) and cells not directly exposed while sensing the infection through other host cells, leading to cell-autonomous and non-cell-autonomous responses, respectively. Cell-autonomous responses include both of the major layers of immunity: pattern-triggered immunity (PTI), initiated by the recognition of microbial molecules by plant cell surface pattern recognition receptors (PRRs), and effector-triggered immunity (ETI), activated by the recognition of effector molecules delivered by pathogens through nucleotide-binding leucine-rich repeat receptors (NLRs) (Jones et al. 2024). Diverse cell-autonomous PTI and ETI responses likely arise from the pre-existing immune potential of individual cells, but the extent and regulatory basis of this variation remain poorly understood.

Non-cell-autonomous immune responses are initiated by endogenous signals released from cells that have already activated their immune responses either in a cell-autonomous or non-cell-autonomous manner. Such indirect immune responses play a crucial role in the plant's overall defense strategy against pathogens, extending protection beyond the initially infected region. These signals can be transmitted through apoplastic and symplastic routes. Non-cell-autonomous responses can be affected by several factors, including the spatial distance from the initially responding cells and the physicochemical nature of signaling molecules. Well-known examples of such responses are systemic acquired resistance (SAR), where a local infection in a leaf sends signals to systemic leaves to confer resistance throughout the plant (Zeier 2021), and localized acquired resistance (LAR), which will be discussed later (Jacob et al. 2023). Cell-cell communications within local infected tissue remains understudied.

(3) Pathogen dynamics

Pathogens are not static entities that simply trigger plant responses in a single, isolated event, but rather dynamic agents that continuously influence plant cells during infection. They move within the host and alter their behaviour at different stages of infection. Many pathogens initially suppress plant immunity for colonization before transitioning to host cell killing. This phase transition does not necessarily occur synchronously across all infection sites. Furthermore, pathogens deploy an array of molecules to manipulate plant responses in diverse ways to enhance their virulence. These molecules can be delivered in a cell-specific manner, adding to the diversity of immune cell states. This molecular and spatiotemporal heterogeneity creates a complex scenario in which plant cells may

Accepted manuscript version of:
Nobori T., “Immune cell states: critical building blocks of the plant immune system” *Cell Host & Microbe*, 2025. DOI: https://doi.org/10.1016/j.chom.2025.06.016

activate immune responses at different times, depending on their exposure to the pathogen. As a result, individual plant cells may simultaneously engage in both cell-autonomous and non-cell-autonomous immune responses, blurring the distinction between these two modes of responses.

Knowledge gaps in plant immune cell states

Examining the current concepts of the plant immune system through the perspective of immune cell states reveals critical knowledge gaps. For instance, despite extensive identification of plant immune components in the past decades, surprisingly little is known about which components are involved in (non-)cell-autonomous responses. Recent advancements in structural biology have greatly enriched our understanding of plant immunity, particularly with respect to the activation mechanisms of PRRs and NLRs. Nevertheless, the full chain of molecular events immediately downstream of pathogen ligand recognition by immune receptors (i.e., cell-autonomous immune responses) is still enigmatic. Recent studies suggested that PTI components are crucial for the full activation of ETI, and conversely, ETI can upregulate PTI components (Yuan et al. 2021). This highlights the interconnectedness of the two immune pathways, but raises further questions: are these interactions occurring within the same cell, or are they mediated by signals exchanged between different cells? How does PRR or NLR activation shape the spatial patterning of immune responses? Careful dissection of cell-autonomous and non-cell-autonomous immune responses is key to answering these questions.

Bulk omics quantitatively measure immune responses, but interpreting these tissue-level measurements through the lens of cell states raises a new question: do these responses reflect broad changes across all cells, or are they primarily driven by shifts within specific cell states? Resolving this distinction is essential for understanding the cell state-specific roles of immune pathways and how these pathways interact as part of broader immune networks. In a similar vein, caution is needed when using “immune marker gene” expression as an indication of immune activation, as different marker genes might be expressed in different cell states, i.e., “immune activation” is not a single phenotype.

As noted in the previous section, cell-cell communications play a pivotal role in non-cell-autonomous immune responses. Multiple mechanisms of immune signal transduction have been identified, including signaling through plasmodesmata (PD), the propagation of calcium (Ca^{2+}) and reactive oxygen species (ROS) waves, and the transmission of electric signals. Damage-associated molecular patterns (DAMPs) and phytocytokines also serve as signaling molecules that can activate non-cell-autonomous immune responses when perceived by receptors in neighboring cells. The SAR pathway

Accepted manuscript version of:
Nobori T., “Immune cell states: critical building blocks of the plant immune system” *Cell Host & Microbe*, 2025. DOI: https://doi.org/10.1016/j.chom.2025.06.016

similarly has the potential to mediate local cell-cell communication. It is also possible that defense phytohormones such as salicylic acid and jasmonic acid move between cells. However, the roles of these processes in the emergence, maintenance, and transitions between immune cell states remain largely uncharted.

Hypersensitive response associated with cell death is a hallmark of strong plant immunity. While death is a state, its role in immune cell states requires further exploration. How much do dead cells actively participate in immune processes, and are they merely consequences of prior immune activation? Dead cells may release molecules, including DAMPs, to activate neighboring cells, but the spatiotemporal dynamics of this process remain unclear. While macroscopic cell death has been extensively documented, microscopic cell death is less understood. It is plausible that a small subset of cells, such as those targeted by pathogen effectors, die early and signal surrounding cells to amplify immune responses. Understanding which cells undergo cell death, the mechanisms driving this process, and their influence on their cell states is key to understanding plant immune complexity.

The links between plant immune cell states and pathogen localization and activity remain poorly understood. A study showed that an immunity-related gene is specifically suppressed in the cells penetrated by the oomycete pathogen *Hyaloperonospora arabidopsidis* (Caillaud et al. 2013). Can immune cell states be predicted simply by the distance from pathogen cells? Are there specific plant cell states that create favorable niches for pathogens? When and what types of effectors and other molecules are delivered to specific cell states? Addressing these questions will require simultaneous in situ monitoring of plant and pathogen responses.

Emerging understanding of plant immune cell states

Recent studies using cell biology and genomics have started to reveal cell states involved in immunity. Here, I highlight several studies as examples rather than a comprehensive literature survey.

Zhou et al. conducted microscopic analyses of immune reporter plants to show that damage in a root epidermal cell induces state change in neighboring cortex cells characterized by the induction of an immune receptor, thereby conferring immune responsiveness (Zhou et al. 2020). This exemplifies an immune potential shaped by pathogen attack in a non-cell-autonomous manner. While the detailed molecular nature of the damage-induced cell state remains elusive, single-cell and spatial omics analysis can provide a comprehensive picture of the emergence of these cell states. Additionally, how a damaged cell transmits signals to neighboring cells is an outstanding question.

Accepted manuscript version of:
Nobori T., “Immune cell states: critical building blocks of the plant immune system” *Cell Host & Microbe*, 2025. DOI: https://doi.org/10.1016/j.chom.2025.06.016

Single-cell RNA-seq analyses of Arabidopsis leaves infected by bacterial and fungal pathogens revealed spatially distinct transcriptional cell states within infected tissues (Tang et al. 2023; Zhu et al. 2023). Zhu et al. identified cell populations enriched with known immunity and susceptibility marker genes that emerge at different timings after bacterial infection (Zhu et al. 2023). Tang et al. observed high basal expression of a specific type of NLRs in vascular-related cells and their induction upon fungal infection, highlighting the relevance of distinct immune potential (Tang et al. 2023). They also showed that both infected and uninfected cells induce transcriptional changes but in distinct ways, providing a clue to dissect (non)cell-autonomous responses.

Another study employed time-course single-nucleus multiomics (transcriptome and epigenome) and spatial transcriptomics to investigate Arabidopsis leaves infected by bacterial pathogens (Nobori et al. 2025). This study uncovered novel immune cell states, including the primary immune responder (PRIMER) cell, initially identified by integrating single-cell RNA-seq clustering, pseudotime trajectory analysis, and spatial transcriptomics. PRIMER cells emerge at the nexus of immune-active regions in infected leaves. Surrounding the PRIMER cells is another distinct population, termed bystander cells, exhibiting unique transcriptomic and epigenomic profiles. These findings fit the concept of LAR. Jacob et al. recently revisited this concept and proposed that ETI suppresses pathogen growth by confining pathogen cells in local infection sites (i.e., near PRIMER cells) by deploying immune active regions surrounding them (i.e., bystander cells) (Jacob et al. 2023). Many questions remain: (1) Are PRIMER cells the ones initiating cell-autonomous immune responses? (2) Are there more than one bystander state based on their spatial relationships with pathogens and PRIMER cells? (3) What are the signals exchanged between PRIMER and bystander cells?

A roadmap to investigate plant immune cell states and their interactions with microbes

In this section, I discuss how emerging technologies will accelerate the research of plant immune cell states by focusing on their identification, dissection of regulatory mechanisms, manipulation, and functional characterization (Figure 1B).

Single-cell RNA-seq is a powerful strategy for identifying immune cell states (Tang et al. 2023; Zhu et al. 2023; Nobori et al. 2025). The findings, however, should be verified with orthogonal methods, including spatial approaches. As the diversity and complexity of cell states require simultaneous analysis of many genes, spatial transcriptomics with cellular resolution is a promising approach. Single-cell omics data can guide candidate gene selection for imaging-based targeted spatial transcriptomics, resulting in a distilled list of genes with robust cell state identification. Since most

spatial transcriptomics platforms lack 3D resolution or reliable microbial mapping, traditional transgenic reporter lines will be useful to further validate the most promising cell state marker genes with real-time 3D imaging. Co-visualising fluorescently labelled microbes clarifies the spatial relationships between immune cell states and pathogen distribution. As an alternative to time-consuming transgenic reporter approaches, emerging multiplexed in situ hybridization-based approaches allow 3D spatial analysis of multiple genes without requiring transgenic lines (Nobori 2025). I propose seamless integration of single-cell RNA-seq, spatial transcriptomics, and 3D imaging efficiently and robustly identifies plant immune states with detailed molecular information (Figure 1B).

How cell state-specific gene expression is regulated is another fundamental question. Adding an epigenome perspective in cell state analysis offers a powerful solution. Single-cell multiomics that combines scRNA-seq and single-cell assay for transposase-accessible chromatin sequencing (scATAC)-seq enables direct integration of gene expression with chromatin accessibility at the single-cell level (Figure 1B). A recent study of mice employed single-cell multiomics and spatial transcriptomics combined with massively parallel reporter assays and deep learning approaches to identify cis-regulatory elements (CREs), such as enhancers, that control cell type-specific gene expression (Bravo González-Blas et al. 2024). Applying such approaches to plant systems holds promise for unravelling the gene regulatory networks (GRNs) underlying individual plant immune cell states.

Over the past decades, various genetic resources, including mutant plants of key immune components, have been generated through forward and reverse genetic screening. Single-cell and spatial omics approaches are particularly powerful in this context because they can be applied directly to these existing mutant lines without the need to generate additional transgenic reporters. For instance, comparing cell state distribution and responses of individual states between wild-type and mutant plants can explain, from a cellular perspective, why certain mutants exhibit increased or decreased resistance to pathogen attack.

Beyond using existing mutants, defining cell states and revealing their regulatory mechanisms opens the door to precisely manipulating specific cell states, which is critical in investigating their function (Figure 1B). A simple way of testing the function of a cell state is genome editing of target cell state-specific GRN components (such as TFs, downstream target genes, or CREs). More precise genetic manipulation may be possible by inducing CRISPR components in specific cell states using cell state-specific CREs or promoters. Cell state-specific CREs can also be used to express a gene of interest in a specific cell state to test its context-dependent function. Precise manipulation of a cell population could also be achieved using optogenetic tools, provided that new developments in these technologies allow for high spatial resolution or even single-cell manipulation. Additionally, microbes

Accepted manuscript version of:
Nobori T., “Immune cell states: critical building blocks of the plant immune system” *Cell Host & Microbe*, 2025. DOI: https://doi.org/10.1016/j.chom.2025.06.016

could be employed to manipulate specific cell populations. For instance, engineered transcription activator-like (TAL) effectors delivered by bacteria could be used to induce specific genes or genetic circuits in target plant cells, thus providing a means to study cell-autonomous immune responses. Such cell state-specific manipulation can be combined with single-cell and spatial omics to reveal how perturbations in a cell state affect other cell states, potentially revealing cell-cell communication mechanisms.

Conclusions and future perspectives

Cellular specialization and division of labor are universal phenomena in multicellular organisms and the community of unicellular organisms to achieve high-level tasks and increase the chance of survival. Instead of evolving specialized immune cells, emerging evidence suggests that plant immunity operates as a complex multicellular network, with inducible and diverse cell states with specific functions coordinating defense. We are entering an exciting era where integrating new technologies brings molecular and cellular views of the plant immune system together to uncover the full picture of this complex system. Current research on the plant immune system predominantly focuses on the leaves and roots of model plants. Expanding single-cell transcriptome and epigenome atlases across whole plant bodies and diverse species will reveal the full spectrum of immune cell states.

In addition to transcriptomic and epigenomic analyses, investigating protein and metabolic dynamics during cell state transitions represents another crucial area for future research. For instance, in *Arabidopsis thaliana*, metabolically specialized vascular cells such as S-cells, which store glucosinolates, and adjacent myrosin cells, which accumulate myrosinase, illustrate how spatially coordinated metabolic cell states contribute to defense (Burow and Halkier 2017). Additionally, recent discoveries identifying metabolites that directly suppress pathogen virulence (Miao et al. 2025) prompt an important question: Which specific cell states produce these metabolites, and how do they contribute to pathogen suppression? High-resolution spatial protein/metabolite profiling promises to address such questions. For a comprehensive overview of emerging single-cell/spatial omics technologies and the potential of data multimodal data integration, see (Nobori 2025).

Commitment to an immune cell state affects the non-immune functions of the cell, as well as those of neighboring cells. Thus, the understanding of immune cell states should not be isolated from their interactions with other cell states of functional importance. At the tissue level, immune activation is known to often negatively affect plant growth and abiotic stress responses—phenomena referred to as trade-offs. Although often attributed to energetic costs or evolutionary constraints in signaling

Accepted manuscript version of:
Nobori T., “Immune cell states: critical building blocks of the plant immune system” *Cell Host & Microbe*, 2025. DOI: https://doi.org/10.1016/j.chom.2025.06.016

network architectures, the exact mechanisms underlying these trade-offs remain poorly understood and debated. Does immune activation inhibit growth because immune-activated cells themselves reduce their capacity for division and expansion, or because they influence the growth potential of neighboring cells? Exploring how immune cell states interact with cell states regulated by developmental programs and environmental stimuli is a critical open question. Addressing this will enable the precise engineering of cell states to enhance immune functions while minimising negative impacts on growth and stress tolerance. Such advancements in cellular engineering are crucial for optimising plant performance and producing resilient crops in the face of climate change.

Accepted manuscript version of:
Nobori T., “Immune cell states: critical building blocks of the plant immune system” *Cell Host & Microbe*, 2025. DOI: https://doi.org/10.1016/j.chom.2025.06.016

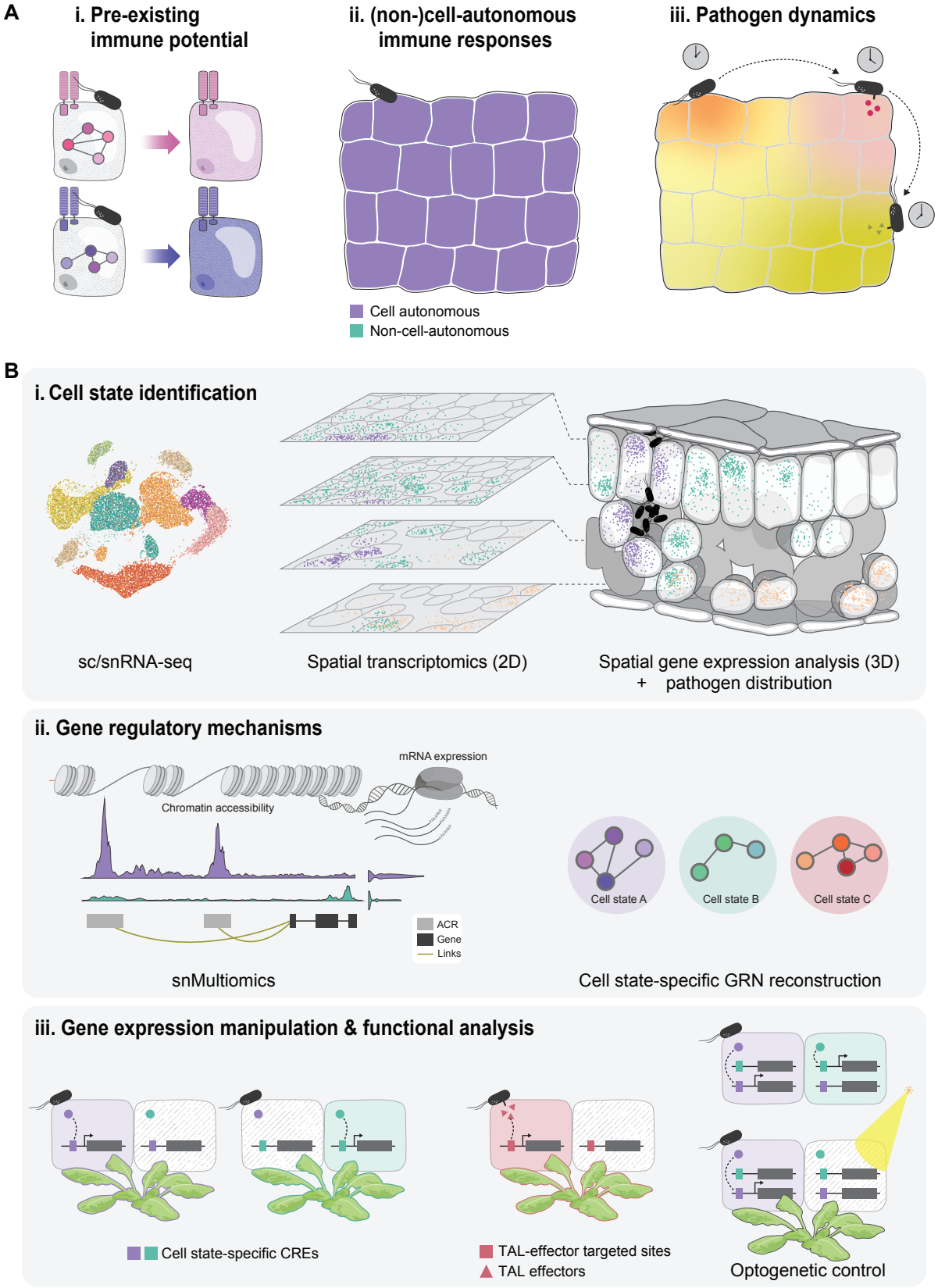

Figure 1.

(A) Factors influencing immune cell state diversity. (i) Pre-existing immune potential. Basal cell-specific expression of immune components and molecular networks can lead to diverse immune responses. (ii) Cell-autonomous and non-cell-autonomous immune responses are triggered through distinct mechanisms. (iii) Pathogen dynamics. Pathogens move spatially over time and modify their interactions with host cells.

(B) Approaches for studying immune cell states. (i) Cell state identification: Combining single-cell (sc)/single-nucleus (sn)-RNA-seq with 2D spatial transcriptomics and 3D spatial analyses, integrated with pathogen distribution, maximizes molecular and spatiotemporal resolution for identifying distinct cell states. (ii) Gene regulatory mechanisms. snMultiomics integrates transcriptomic and epigenomic data at single-cell resolution, connecting accessible chromatin regions (ACRs) with gene expression to reconstruct cell state-specific gene regulatory networks (GRNs). (iii) Gene expression manipulation and functional analysis. Cell state-specific transgene expression can be achieved using cell state-specific cis-regulatory elements (CREs) or pathogen-derived transcription activator-like (TAL) effectors. Additionally, targeted manipulation of specific cell states may be accomplished through optogenetic methods.

Acknowledgements

I apologize to all authors whose valuable work could not be included in this review due to space constraints. I thank Hsuan Pai for contributing to the figure design, and Jeffery Dangl, Jonathan Jones, Kenichi Tsuda, Pierre Jacob, and members of the Nobori lab for their critical reading of the manuscript and insightful discussions. I also thank the four reviewers for their constructive feedback. This work was supported by a grant to T.N. from The Gatsby Charitable Foundation and Biotechnology and Biological Sciences Research Council (BBSRC) BB/Y002997/1.

Declaration of interests

The author declares no competing interests.

References

Bravo González-Blas C, Matetovici I, Hillen H, Taskiran II, Vandepoel R, Christiaens V, Sansores-García L, Verboven E, Hulselmans G, Poovathingal S, et al. Single-cell spatial multi-omics and deep learning dissect enhancer-driven gene regulatory networks in liver zonation. Nat Cell Biol. 2024:**26**(1):153–167.

Burow M and Halkier BA. How does a plant orchestrate defense in time and space? Using glucosinolates in Arabidopsis as case study. Curr Opin Plant Biol. 2017:**38**:142–147.

Caillaud M-C, Asai S, Rallapalli G, Piquerez S, Fabro G, and Jones JDG. A downy mildew effector attenuates salicylic acid-triggered immunity in Arabidopsis by interacting with the host mediator complex. PLoS Biol. 2013:**11**(12):e1001732.

Fröschel C and Dröge-Laser W. Hidden in the parts: how the cell type perspective reveals novel insights into plant-microbe interactions. Mol Plant. 2023. https://doi.org/10.1016/j.molp.2023.07.014

Jacob P, Hige J, and Dangl JL. Is localized acquired resistance the mechanism for effector-triggered disease resistance in plants? Nature Plants. 2023:1–7.

Jones JDG, Staskawicz BJ, and Dangl JL. The plant immune system: From discovery to deployment. Cell. 2024:**187**(9):2095–2116.

Miao P, Wang H, Wang W, Wang Z, Ke H, Cheng H, Ni J, Liang J, Yao Y-F, Wang J, et al. A widespread plant defense compound disarms bacterial type III injectisome assembly. Science. 2025:**387**(6737). https://doi.org/10.1126/science.ads0377

Nobori T. Exploring the untapped potential of single-cell and spatial omics in plant biology. New Phytol. 2025. https://doi.org/10.1111/nph.70220

Nobori T, Monell A, Lee TA, Sakata Y, Shirahama S, Zhou J, Nery JR, Mine A, and Ecker JR. A rare PRIMER cell state in plant immunity. Nature. 2025:1–9.

Rusnak B, Clark FK, Vadde BVL, and Roeder AHK. What Is a Plant Cell Type in the Age of Single-Cell Biology? It's Complicated. Annu Rev Cell Dev Biol. 2024. https://doi.org/10.1146/annurev-cellbio-111323-102412

Tang B, Feng L, Hulin MT, Ding P, and Ma W. Cell-type-specific responses to fungal infection in plants revealed by single-cell transcriptomics. Cell Host Microbe. 2023:**0**(0).

Accepted manuscript version of:
Nobori T., "Immune cell states: critical building blocks of the plant immune system" *Cell Host & Microbe*, 2025. DOI: https://doi.org/10.1016/j.chom.2025.06.016

https://doi.org/10.1016/j.chom.2023.08.019

Yuan M, Ngou BPM, Ding P, and Xin XF. PTI-ETI crosstalk: an integrative view of plant immunity. Curr Opin Plant Biol. 2021:**62**:102030.

Zeier J. Metabolic regulation of systemic acquired resistance. Curr Opin Plant Biol. 2021:**62**:102050.

Zhou F, Emonet A, Dénervaud Tendon V, Marhavy P, Wu D, Lahaye T, and Geldner N. Co-incidence of Damage and Microbial Patterns Controls Localized Immune Responses in Roots. Cell. 2020:**180**(3):440-453.e18.

Zhu J, Lolle S, Tang A, Guel B, Kvitko B, Cole B, and Coaker G. Single-cell profiling of Arabidopsis leaves to Pseudomonas syringae infection. Cell Rep. 2023:**42**(7):112676.