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## Editorial overview: Lymphocyte development and activation: Lymphocytes, integrators of information

Jeroen Roose and Sidonia Fagarasan

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### Jeroen Roose



Department of Anatomy, University of California, San Francisco (UCSF), CA, USA  
e-mail: [jeroen.roose@ucsf.edu](mailto:jeroen.roose@ucsf.edu)

Jeroen Roose is an associate professor at UCSF. His laboratory has contributed to the concept that lymphocytes can transduce analog or digital Ras-MAP kinase signals depending on the strength of receptor signal and the choice of Ras activator. His team continues to investigate how perturbed Ras-kinase signals underlie autoimmune diseases and cancer (<http://rooselab.ucsf.edu/Home.html>).

### Sidonia Fagarasan



Laboratory for Mucosal Immunity, Center for Integrative Medical Sciences, RIKEN Yokohama Institute, Japan  
e-mail: [sidonia.fagarasan@riken.jp](mailto:sidonia.fagarasan@riken.jp)

Sidonia Fagarasan obtained her MD at the University of Medicine and Pharmacy, Cluj, Romania in 1990 and PhD at the Kyoto University in 2000. She worked as a postdoctoral fellow in the lab of Tasuku Honjo at the Kyoto University, where she became interested in studying the impact of

Research on lymphocyte development and activation has matured to a level of sophistication that we can start to integrate multiple instructions coming from various players and understand how these instructive ‘networks’ govern lymphocyte function. The collection of reviews in this edition of Current Opinion in Immunology focuses on the complexity of intracellular cues that overcome a signal threshold paired with changes in metabolic programs. In the second section recent advances on cell-extrinsic factors and cell–cell interactions as regulators of lymphocyte function are highlighted.

Stimulation of antigen receptors on lymphocytes leads to triggering of intracellular signaling pathways that are connected to form signaling networks. The topology and dynamic nature of these networks are only just emerging. [Helou and Salomon](#) provide an overview of the current state of high-resolution mass spectrometry and how it has enabled to understand these networks in a quantitative and qualitative manner. Their phosphoproteomic approaches on T cells have provided us with a blueprint of the TCR signaling network and an appreciation of its dynamic nature through the analysis of temporal changes in protein phosphorylation. They discuss the challenges of quantitative phosphoproteomic in primary lymphocytes and how these may be met via studies of mouse models with genetic tags that allow for efficient mass spec or through mass cytometry (CyTOF), a new technique that couples flow cytometry single cell resolution with the resolution of mass spec. Resolving the identity of these networks may have future clinical impact by offering insights how to modulate T cell function by tweaking these signaling networks.

Understanding the topology and dynamics of antigen receptor signaling networks also provides the opportunity to understand, at a fundamental level, how signaling thresholds are overcome and how biologically relevant low-affinity signals are distinguished from noise. [Zikherman and Au-Yeung](#) discuss the concept of analog to digital signal transformation, the role of feedback loops herein, and the need for biochemical analyses that resolve signals in individual lymphocytes within a pool of cells. They discuss how reporters, such as the *Nur77* reporter mouse models that integrate signals in a cumulative manner, have enhanced our understanding how strength and duration of T cell receptor (TCR) signals drive proper T cell development and function. They discuss their elegant studies where they have paired a *Nur77*-eGFP reporter with a *Zap70* kinase inhibitor system that reveal that a signaling threshold need to be met and that alterations in the TCR signals do not affect the threshold but impact the number of T cells within a pool that successfully overcome this threshold.

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antibody diversification in regulating the gut microbiota. Since 2002 she heads the Laboratory for Mucosal Immunity at the RIKEN Yokohama. Her lab focuses on the question of how the immune system mediates the complex host-bacterial mutualism and how the adaptive immune system interacts via the microbiome with other physiological systems of the body.

The concept of proportions of T cells that successfully overcome a threshold to become functional brings up the question how these thresholds are set. Recent work has pointed to negative regulators in the proximal part of the TCR signaling network as modulators of signaling threshold. [Gascoigne and Acuto](#) provide an overview on thymic selection and how THEMIS plays an important role in ligand discrimination. THEMIS only entered the stage of TCR signaling in 2009 after simultaneous identification by several different groups. Despite the clear defect in positive selection of thymocytes in THEMIS-deficient mice a mechanism for this defect has been lacking. They discuss how they uncovered that THEMIS is not a positive regulator of TCR signaling — as was initially anticipated — but a negative regulator and how Ed Palmer's Ova variant system was key for this discovery. They discuss how THEMIS brings in tyrosine phosphatases to inhibit the active proximal TCR signaling components and how this negative feedback loop sets a very sharp threshold that helps explain the precise ligand discrimination by the TCR. They place THEMIS in the context of additional feedback mechanisms in a new model for TCR ligand discrimination during T cell selection.

It has become clear that TCR-induced activation of T cells must be paired with other cellular changes, for instance to meet the increased metabolic demands. In the last section on T cells, [Delgoffe and Powell](#) discuss recent insights in metabolic signaling in T cells. It has been established that activated T cells upregulate expression of glucose transporters and burn glucose as fuel whereas quiescent naïve and memory T cells choose lipids as predominant fuel source. They discuss how TCR signals influences switching between metabolic programs but also how the metabolic pathways influence T cell function. The interplay between fuel and function is a very active research area and they discuss their own work on the TCR signaling mTOR complexes, mTORC1 and mTORC2, which simultaneously function as a nutrient sensor and therefore sit at the nexus of TCR activation and metabolism. Lastly, mTOR is not the only nutrient sensor in T cells and several other sensors are discussed in the context of metabolic processes such as glutamine metabolism, oxygen sensing, and autophagy.

Vertebrates have evolved sophisticated mechanisms to recognize and respond to an unlimited variety of foreign antigens. Diversification of the immune repertoire is required not only to fight infections but also to maintain the homeostasis, including the diversity of associated microbial communities present at the mucosal barriers. During embryonic life, B cell development occurs at different locations, starting in the fetal liver and toward the end of gestation in the bone marrow and spleen. [Wesemann and colleagues](#) provide an overview on relationships between the timing and location of B cells development and generation of a functionally 'fit' immunoglobulin repertoire. They outline the B cell development and the selecting forces that drive and regulate the antibody repertoire. They discuss the early postnatal window during which B cell development also occurs in the gut driven by interaction with local antigens mainly derived from colonizing bacteria. Indeed, the gut constitutes a very dynamic environment exposed to antigens derived from the residential microbes. It seems that the dialog between bacteria and the adaptive immune cells begins with immature B cells developing in the gut and undergoing IgL-chain gene segment rearrangement thus generating B cells with distinctive antigenic repertoire shaped by local antigens. Such local B cell development and editing may be part of a finely tuned signaling program ensuring a state of hypo-responsiveness against dietary antigens and commensal bacteria.

In addition to B and T cells, proper functioning of the adaptive immune system particularly at the interface between host and the environment, requires additional cells called innate lymphoid cells (ILCs). These are cells that do not possess somatically recombined receptors, but express transcription factors and cytokines that mirror those present in various types of helper T cells. Currently ILCs are classified into three classes: ILC1 producing Th1-cytokines, ILC2 releasing large amounts of Th2-type cytokines like IL5 and IL13, and ILC3 cells, which in addition to their role for the development of lymphoid tissues, secrete IL17 and IL22, cytokines typically produced by Th17 cells. As innate source of such effector cytokines, ILCs have roles in early defense against infections. However, more recently ILCs begin to be regarded also as regulatory cells bridging the innate and adaptive immune responses and coordinating various aspects of adaptive immune responses. In this issue, [Magri and Cerutti](#) give an overview of the functional properties of ILC3, and discuss how ILC3 integrate stromal and myeloid signals to coordinate systemic and mucosal T cell-dependent and independent antibody responses. They propose that ILC3 might represent ancestral inducer-effector cells capable to coordinate both primitive and evolutionarily evolved pathways generating protective antibodies.

Certainly one sophisticated pathway specialized in generation of durable antibody responses involves formation of anatomically distinct structures called germinal centers (GCs). The GCs are special sites where diversification and selection of antibody repertoires takes place. Unlike the generation of the primary B cell repertoire, which depends on the RAG, the second wave of diversification of the B cell repertoire depends on the AID, the enzyme responsible for both SHM and CSR reactions. It is in the GC that B cells diversified upon AID introduced somatic hypermutation (SHM) and selected by antigens and T cells differentiate into memory cells and plasma cells secreting high-affinity antibodies. Most of the plasma cells generated in GC of peripheral lymphoid tissues end up in the bone marrow where, when finding the

right niche, they become long-lived plasma cells. Exactly what factors are responsible for generation and maintenance of such long-lived plasma cells is still unclear. In this issue [Kometani and Kurosaki](#) outline the multiple steps required for generation and maintenance of immunological memory. They are discussing the cell-intrinsic and cell-extrinsic factors responsible for differentiation of GC B cells into plasmablasts and survival of plasma cells in the bone marrow. They discuss the existence of a preprogrammed potentiation controlled by transcription factors, such as Blimp-1 and ZBTB20, for durable and protective antibody responses.

Thus, SHM and selection of B cells in GCs generate antibodies with high affinity and specificity for the immunizing antigen. However, the generation and persistence of memory cells with self-reactive properties needs to be avoided in order to prevent autoimmune diseases that may have with life-threatening consequences. Selection of autoreactive B cells can be the consequence of abnormalities in each of the cellular and molecular components involved in GCs. In this issue, [Rowlings and colleagues](#) highlight recent studies suggesting that B cells play key roles in autoimmune pathogenesis. They emphasize that altered B cell signaling may be sufficient to initiate and maintain GCs where autoimmune antibodies are generated. They propose a model in which dual TLR and self-antigen specific BCR signals, together with cytokine mediated feed-forwarding signals, generate spontaneous GCs. In such GCs, activated B cells promote activation of self-reactive T cells and facilitate both affinity maturation of B cells and generation of plasma cells secreting autoreactive antibodies. Indeed, genetic alterations in specific antigen receptor signaling effectors that initiate autoimmune germinal center responses were found in both mouse and man.

In summary, we hope that the reviews in this edition of *Current Opinion in Immunology* highlight a variety of different aspects regarding the complexity of lymphocyte activation to the readers and reveal some of the tools and directions for future research on lymphocyte development and activation.