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Editorial overview: Lymphocyte effector subsets: blurring the frontiers

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The VDJ recombination process shapes a large pre-immune repertoire of lymphocytes which, apart from a few exceptions, display naive features as they migrate out of primary lymphoid organs. Antigenic stimulation, either from exogenous sources or from microbiota origin then induces various immune responses, constituting innate-like activated cells with global surveillance function, short-lived effectors for immediate responses or long-lived memory cells with pathogen-specific recall potential. Distinct TCR, BCR, transcription factors, cytokine or chemokine secretion profiles or chemokine receptors are classically used to define lymphocyte subsets and their distinct effector functions. This issue puts together a set of reviews that all address the complex issue of subset delineation or of their commitment, or discuss new effector functions of well-defined subsets.

Sprent *et al.* discuss the role of Tregs cells in controlling the slow conversion of naive CD4 T cells into 'virtual memory' (or memory phenotype) T-cells. They discuss the notion that such conversion is largely, though not entirely, driven by self-antigens, since it still occurs in germ-free and antigen-free mice (fed a low molecular weight diet), and occurs continuously during adulthood. Multiple mechanisms appear to take part in this control, including stripping of co-activation molecules, secretion of inhibitory cytokines, and, only in part, a diverse TCR repertoire.

A second report on Tregs discusses their potential in organ regeneration. In the mouse, previous reports have described a tissue-repair function of Tregs mediated by paracrine signals like amphiregulin, which stimulate tissue progenitors. Kikuchi discusses recent data which addressed the regenerative potential of Tregs in zebrafish, a species that shows a robust capacity to regenerate complex tissue structures following multiple types of injuries. These studies first established a 'classical' immunosuppressive role of Tregs in this species, controlling inflammation and immune homeostasis. They further revealed the astonishing capacity of zebrafish Tregs to produce regenerative factors specific to the site of injury, like

neuregulin 1 for the heart and insulin-like growth factor 1 for the retina. Understanding the triggering signals of such tissue-specific secretion might open new avenues for manipulating Tregs for repair purposes.

There are two forms of persistent parasitism that confront our immune system. Infectious agents in many different forms often establish a chronic presence that challenges the immune system to continuously respond or alternatively, establish a form of tolerance. The latter is often selective given the specter of immunopathology and the futility of an extended reaction against a parasite evolved to maintain infection for the natural life of the host. In contrast, neoplasia evolves *de novo* under pressure only to grow and metastasize as fast as possible, without regard to transmissibility or host longevity. Marcel and Hedrick describe this dichotomy and the how our immune system may have evolved to accommodate the former even though this regulation is maladaptive for the latter. Still, the differentiation of T cells includes a population that retains stem cell-like qualities and an ability to reengage chronic parasitism—even that of malignant cancers. The gene expression that is central to this long-responsive memory population depends upon the expression of the transcription factor, FOXO1.

While commitment to a distinct lineage starts with the activation of a transcription factor and an ensuing network of activated and repressed genes, chromatin dynamics relays the initial trigger, and fate decisions are maintained at the epigenetic as well as at the genetic level. Pace and Amigorena discuss the regulation of such chromatin states and the role of epigenetic marks, mobilizing histone modifiers, DNA methylases, histone readers, in stabilizing cell fate decisions: stemness (or memory), for example, is linked to a more accessible chromatin state allowing for multiple programming choices, while T-cell exhaustion features an epigenetic stability that limits transcriptional rewiring. Such closed chromatin configuration may compromise PD1 blockade treatments, unless combined with DNA methylation inhibition that favors T-cell reprogramming. The epigenetic code clearly adds to the interclonal and intra-clonal heterogeneity of T cells, and only starts to be deciphered.

Tissue residency is a relatively recent notion adding to the complexity of the memory T cell subset landscape (resident memory T cells or T_{RM}). Such memory T cells residing in non-lymphoid tissues, notably at barrier sites, rapidly alert innate and adaptive immune cells of a reinfection event, can themselves participate in the response against the pathogen, and join transiently the circulation before resettling in tissue. This apparent flexibility of function leads Masopust *et al.* to interrogate the definition of effector and memory subsets, often borrowed from linear developmental schemes, for a more stochastic behavior whereby the fate

of a given ‘experienced’ T cell could fluctuate along a path of progressively restricted potentialities, within a continuum of migrational heterogeneity and plasticity. Subsetting T cells thus appears as a practical way to classify diversity, but may be improper at reflecting the inherent heterogeneity of a T cell recall response.

The question of CD4 T cell subsetting is further addressed by Benoist *et al.*, based on the exploding development of single-cell RNAseq approaches, which aim at developing an exhaustive atlas of T cell profiles. However, while such single-cell approaches have indeed resolved a new entity, the ‘Tis’ subset that harbors a distinct interferon signature, the authors underline that clustering based on single cell gene expression profiling often fragments populations harboring similar transcription factor or cytokine signatures. This discussion, together with some specific technical issues related to the use of algorithms that segregate T cells into the multi-colored clusters of a Seurat display, thus re-joins the previous one on the internal heterogeneity of cells issued from previously well-defined subsets, raising the question of the continuity/discontinuity of their trajectories.

Activation drives naive B cells out of their quiescent state, and turns on new energetic demands. Metabolic reprogramming varies along the B-cell activation pathway, with distinct signals triggering various profiles, adapted to provide survival signals, fuel for proliferation, or metabolic adaptation allowing for the massive glycosylation of antibodies secreted by plasma cells. Jellusova *et al.* describes that, while cell activation drives such metabolic changes, there is a bidirectional influence of signal transduction on metabolism and of metabolite sources on B cell fate, making B cells highly responsive to their metabolic environment.

Upon T-dependent antigenic activation, B cell migration and differentiation in germinal centers will lead to multiple rounds of somatic mutation allowing them to diversify their Ig genes. Strikingly, germinal center B cells have multiple differentiation choices that will lead, through distinct antigen and TFH-derived positive selection signals, to their emergence as memory B cells or plasma cells with increased affinity for their cognate antigen, or, alternatively, to their recycling into the germinal center dark zone for further antigen diversification. Brink *et al.* review recent advances in the definition of signals that trigger germinal center B cell commitment to either of this three-way-path, as well as signals that allow the rapid elimination of less-fit B cell clones randomly emerging from the hypermutation process.

IgM B cells that harbor somatic mutations in their Ig genes do not match a single functional entity. Reynaud and Weill discuss recent data focused on IgM ‘memory’ B cells, which reveal

that such antigen-experienced cells that did not undergo isotype switch cover in fact a wide spectrum of ontogenies and functions, both in mice and humans. They can represent classical antigen-specific memory B cells, whose prevalence depends on the nature of the antigenic or infectious trigger, able to respond quickly to new challenges with multiple differentiation outcomes. At the other side of the spectrum, they can achieve innate-like functions, recent data documenting a gut-spleen axis with endows IgM B cells with the capacity to respond to bacterial antigens through cross-reactive recognition of shared glycan epitopes. So far, no simple phenotypic traits or gene expression profile allow the clear delineation of such diverse effector potentials.

The overall picture that emerges from these different reviews is a multi-faceted description of lymphoid subsets: rather than relying on unique cytokines or transcription factors, distinct subsets are further qualified by their tissue-residency, their metabolic status and a combinatorial rather than univocal gene expression profile. High dimensional and single cell technologies are largely contributing to blurring the frontiers between functional entities. Both discussions by Benoist and Masopust pioneer a ‘cloud’ vision of effector subsets whereby flexibility of function would correspond to an array of possible fates. While such description is obviously more complex to apprehend than a simple division of tasks between multiple immune effectors, it may help to integrate a probabilistic vision in the outcomes of immune stimulation, possibly better adapted to understand the diversity of patient’s response in the expanding context of immune interventions.

Claude-Agnès Reynaud is director of research and group leader at Institut Necker-Enfants Malades, Université de Paris. She studies, together, with Jean-Claude Weill, different facets of processes leading to B cell repertoire and memory formation in mice and humans, both in terms of molecular mechanisms of Ig gene diversification and of distinct pathways leading to innate-like or adaptive immune memory.

Dr Hedrick obtained his PhD at UC Irvine working with James Watson on immune response genes and MHC restriction. He carried out postdoctoral studies at the National Institutes of Health working first with Ronald Schwartz, and then with William Paul and Mark Davis. He was recruited to UC San Diego by Richard Dutton, and has been a faculty member there ever since. He was named last year to the inaugural class of Distinguished Fellows of the American Association of Immunologists. Dr Hedrick has studied T cell-mediated immunity, and the means by which T cells recognize antigen peptides bound to MHC molecules, continuing with analyses probing the processes of T cell development. Presently, he has been interested in two aspects of T cell-mediated immunity. One is the means by which T cells perceive and integrate extrinsic information in order to differentiate into subsets needed for pathogen clearance or the equipoise established with persistent viruses. A second is host-pathogen co-evolution that entails understanding immunity through the lens of disease ecology.