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Robust control of the adaptive immune system

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ABSTRACT

The adaptive immune system continually faces unpredictable circumstances yet reproducibly counteracts invading pathogens while limiting damage to self. However, the system is dynamic in nature: many of its internal components are not fixed, but rather, fluctuate over time. This concept is exemplified by αβ T lymphocytes, which vary significantly from cell-to-cell in their spatiotemporal dynamics, antigen-binding receptors, and subcellular protein concentrations. How are reproducible immune functions achieved in the face of such variability? This design principle is known as robustness and requires the system to employ layered control schemes that both buffer and exploit different facets of cellular variation. In this article, we discuss these schemes and their applications to individual αβ T cell responses as well as integrated population level behaviours.

1. Introduction

The adaptive arm of the immune system must continually detect and respond to a diverse range of rare, pathogenic foreign antigens while simultaneously limiting responses towards comparatively abundant self-antigens. However, the system cannot predict with certainty the full spectrum of antigens that a given pathogen will furnish, nor can it predict the precise timing or location at which a given pathogen will invade. To provide effective host defense given these constraints, the individual components comprising the system have evolved to be dynamic in nature. In this regard, αβ T lymphocytes serve as a guiding paradigm. Unlike innate immune cells, which utilize conserved receptors to sense their local environment, each individual lymphocyte harbours a unique antigen binding T cell receptor (TCR) that is generated by an essentially random process, termed V(D)J gene recombination [1]. The net result is twofold: 1) the range of foreign and self-antigens that the collective T cell repertoire can recognize is not fixed within any given organism at any moment in time, and 2) the number of T cells that can recognize a given antigen, known as the precursor frequency, is highly variable.

Individual T cells also vary in position over time; they continually transit through and between secondary lymphoid organs, as well as recirculate between blood and lymph [2]. Given the rates of pathogen replication, these spatiotemporal variations could pose significant risk to the host if rare T cell clones failed to locate rare foreign antigens within an adequate time window. However, even once the appropriate T cell locates cognate antigen, its output response is not necessarily fixed. Indeed, single-cell analysis has revealed striking response heterogeneity within populations of monoclonal T cells recognizing the same antigen [3].

The immense degree of variability within the internal components of the system implies that core immune functions are governed by a series of probabilistic behaviours [4]. From this perspective, understanding how the adaptive immune system reproducibly maintains sensitive detection and responsiveness towards a large breadth of foreign antigens while limiting damage to self is challenging. Undoubtedly, certain properties of the system must exhibit some level of invariance across a wide range of internal parameter values, otherwise the core functions would fail, and the impact to the host would be detrimental. Within the disciplines of engineering and control theory, this design principle is known as robustness: a system maintains a particular function despite fluctuations within its internal components [5]. How is immunological robustness enforced? The recent application of diverse methods, from dynamic and highly multiplexed *in situ* imaging, to emerging single-cell and single-molecule techniques, combined with computational modelling and theory, has revealed novel, often-counterintuitive insights into this question. In this article, we will discuss several control schemes spanning multiple spatial and temporal scales that enable the immune system to achieve robustness with respect to αβ T lymphocyte physiology. These schemes encompass, but are not limited to, spatial architecture and compartmentalization, signal discrimination and amplification, noise filtering, and feedback control.

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2. Shifting through time and space: the search for antigen

Since the precise timing and location of pathogen invasion cannot be predicted, αβ T cells patrol the host, recirculating between blood and lymph, in search of pathogen-derived foreign antigens, which are displayed as peptides bound to molecules encoded in the Major Histocompatibility Complex [MHC] on the surface of antigen presenting cells (APC), predominantly dendritic cells (DC) [6,7]. While this dynamic form of surveillance is necessary for host defense, it introduces significant spatiotemporal variability into the system; T cell positions continually fluctuate over time. For the system to be robust towards this variability, a control scheme must exist that enables rare T cells to locate rare foreign antigens in an efficient, timely, and reproducible manner. The network of lymphatic vessels aids in this process by concentrating tissue-derived DC and soluble antigens into regionalized lymph node organs, constraining the effective search domain of individual T cells. However, mice harbour 22 unique lymph nodes, some of which are present in multiple copies [8]. Moreover, each of these organs is at least 10^7 times the volume of a T cell. Even more striking is the fact that only 1–100 per 10^6 T cells will be specific for a given foreign antigen, which will be presented in rare quantities by only a small fraction of the $\sim 4 \times 10^5$ DC within each lymph node, at least during the early stages of infection [9]. Bearing these numbers in mind, it seems highly improbable for a rare T cell to not only find the correct organ to which the relevant antigen has drained, but also the correct DC within this organ.

This situation embodies a universal problem in search theory: what is the optimal strategy to locate a hidden target within a sizable territory? At one end of the spectrum, T cells could rapidly transit each lymph node, engaging a minimal number of DC. While this strategy would limit detection sensitivity, it would maximize the number of lymph nodes sampled. At the other end of the spectrum, T cells could meticulously scan the full volume of a particular lymph node, combing each DC exhaustively. In this case, T cells would maximize their probability of locating cognate antigen within a single lymph node at the expense of sampling fewer overall [2]. Individual T cells must strike a suitable balance between these two extreme scenarios, settling on an optimal dwell time and search strategy per lymph node. However, these parameters should not be rigid, but rather, adaptable depending on the stage of infection and the local microenvironment within the draining lymph node. In the following section, we discuss how structural and chemical cues influence these search parameters in a manner that promotes robustness with respect to T cell spatiotemporal variation, with a focus on early detection of foreign antigen.

2.1. Search constraints imposed by lymph node architecture

While lymph nodes contain millions of cellular constituents, their unique architecture regulates the localization of specific cell types. As a result, these organs are not well-mixed, random distributions of cells, but in fact, highly compartmentalized. This phenomenon can significantly impact search by constraining the effective volume that cells must survey. In the case of T cells and DC, both constituents localize predominantly to the lymph node paracortex. However, even within this compartment, T cell search domains appear to be constrained. For instance, the paracortex is supported by an underlying filamentous meshwork of fibroblastic reticular cells (FRC), which serves as a scaffold for migrating T cells [10]. Although quantitative details are lacking, we envision that close adherence to these linear filaments restricts the effective volume that T cells must traverse, and additionally, reduces dimensionality. By constraining the degrees of freedom of migration, the effective concentration of T cells likely increases. Conceivably, a higher concentration of motile T cells could promote interactions with antigen-bearing DC, which co-reside along the filaments (Fig. 1A). A similar phenomenon has been described for certain receptors diffusing within the plasma membrane of cells; linear confinement zones structured by the cortical cytoskeleton can restrict both the area and dimensionality of diffusion, increasing the local receptor concentration and collision frequency [11].

Spatial inhomogeneity of cells within the paracortex may also place constraints on search. For example, Ebi2-mediated signalling results in the concentration of $CD4^+$ T cells along the peripheral boundaries of the paracortex while $CD8^+$ T cells appear uniformly dispersed within (Baptista et al., submitted manuscript, Fig. 1B). The biased distribution of $CD4^+$ T cells suggests that they may scan through significantly less volume than $CD8^+$ T cells in their search for cognate antigen. In support of this notion, $CD4^+$ T cells display a mean lymph node dwell time of 12.2 versus 22.2 h for $CD8^+$ T cells, despite both subsets migrating with similar mean velocities [12]. Interestingly, tissue-derived DC most effective at processing antigen for MHC class II molecule display, and therefore, most efficient at presenting antigen to $CD4^+$ T cells, also concentrate within the periphery of the paracortex [13–15]. Collectively, these results suggest that although T cell localization continually fluctuates in time and space, the lymph node can buffer these variations by directing cellular localization in a manner that supports efficient antigen detection, and therefore, robustness.

2.2. Search constraints imposed by inflammation

Pathogen invasion is accompanied by inflammatory input signals that accumulate within the draining lymph node, and consequently, modulate search. These inputs can promote entry into, and restrict egress out of the lymph node, effectively increasing the localized T cell precursor frequency. For example, pathogen-derived LPS or DNA can remodel the arteriole feeding the draining lymph node. The resulting increase in blood flow correlates with up to a ~ 5 fold increase in the rate of entry of naïve T cells, increasing the fraction of the repertoire available for antigen engagement [16]. Concomitantly, inflammatory input signals drive transient expression and trafficking of the C type lectin-like protein, CD69, to the T cell plasma membrane. While the mechanism remains unclear, CD69 is generally thought to antagonize the sphingosine-1-phosphate receptor (S1PR1), which binds sphingosine-1-phosphate (S1P) and promotes T cell egress from the lymph node [17]. In this way, T cells are transiently trapped, leading to prolonged dwell times. The combination of increased entry and decreased egress likely accounts for the fact that the recruitment of antigen-specific T cells to the draining lymph node is near complete within the first 72 h of infection [18]. Thus, inflammation can concentrate rare T cells and restrict their search domain to a single lymph node, enhancing the probability of locating cognate antigen.

2.3. Intranodal migratory patterns and search dynamics

In addition to spatial considerations, the motility and migratory patterns of individual T cells within a lymph node are essential to their dwell time. The recent advancements in two-photon intravital microscopy have revealed critical insights into these parameters. By reconstructing discrete cellular trajectories comprised of individual step displacements as a function of time, several studies have described T cell migration *in vivo* as an apparent “random walk”, whereby each cell moves stochastically, independent of its previous step [19,20]. The application of mathematical, diffusion-based models has attempted to further classify this random walk behaviour. In this regard, the mean squared displacement (MSD) of each trajectory is commonly used to relate T cell motility with one of two forms of diffusion: 1) “normal diffusion”, whereby cells move in a Brownian-like fashion and the MSD scales linearly with respect to time, or 2) “anomalous diffusion”, whereby cells move in either a sub-diffusive or super-diffusive fashion, and the MSD scales non-linearly with respect to time [21]. With this approach, many experimental studies have suggested that normal diffusion is the predominant mode of T cell migration, although glimpses of sub-diffusive and super-diffusive behaviours have been documented