



In vivo imaging of adaptive immune responses to viruses

Marco De Giovanni and Matteo Iannacone

Viral infections represent a major threat for mankind. The adaptive immune system plays a key role in both viral clearance and disease pathogenesis, and, accordingly, understanding how lymphocytes interact with different viruses is critical to design more effective vaccination and therapeutic strategies. The recent advent of intravital microscopy has enabled the real-time visualization of the complex interplay between viruses and the ensuing adaptive immune response in living organisms. Here, we will review the most significant recent insights on antiviral adaptive immune responses obtained through intravital imaging. We will also discuss what challenges lie ahead and what we think are the most promising areas for future research.

Address

Division of Immunology, Transplantation and Infectious Diseases and Experimental Imaging Center, IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan 20132, Italy

Corresponding author: Iannacone, Matteo (iannacone.matteo@hsr.it)

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Introduction

Adaptive immune responses play a crucial role in antiviral immunity, as they mediate viral clearance or containment, they contribute to tissue damage, and they are essential for preventing reinfection and for the protection conferred by the available vaccines. In order to mount a successful adaptive immune response against a virus, lymphocytes need to move within distinct organs and tissue niches, where they interact with many different cell types that influence their behavior and function. Since no *in vitro* methodology can fully capture the myriad of physical and chemical cues that influence cell behavior in tissues, several groups have started to utilize intravital microscopy to visualize the dynamics of antiviral immunity as it happens in real time *in vivo* in an organism [1,2]. The idea is relatively simple: an experimental animal is anesthetized and positioned on a suitable stage so that a particular organ can be microsurgically prepared for

microscopic viewing [1,2]. Because of greater resolving power, increased depth penetration and reduced phototoxicity, multiphoton lasers are now the preferred option for most intravital imaging studies; however, due to generally higher temporal resolution, single photon-based epifluorescent techniques are still used for studying events that occur rapidly, such as the intravascular adhesion of leukocytes in superficial sinusoids of the liver [3**].

We will review here how intravital imaging has improved our understanding of adaptive immune responses to viruses. Specifically, we will discuss recent studies pertaining to the priming of antiviral B cells and T cells within secondary lymphoid organs; moreover, using the liver as a paradigmatic example, we will discuss how effector T cells exert their antiviral function in the periphery. For a thorough discussion of advances obtained through the use of intravital imaging pertaining to viral spread, innate antiviral immunity and adaptive immune responses to viruses that infect peripheral organs other than the liver (e.g. skin, lung, central nervous system, gut, pancreas), we refer readers to recently published reviews [4–6].

Priming of antiviral B cells

Using intravital imaging, several pioneering studies have begun to elucidate how B cells encounter antigen and become activated in lymph nodes [7–10]. Regardless of whether these studies were conducted with intact viral particles or with inert particulate antigens, they all identified the lymph node subcapsular sinus (SCS) as an important area for early B cell-antigen encounter [11,12,13**,14**]. The SCS collects unfiltered lymph from afferent lymph vessels and hosts macrophages (SCS macrophages) that are attached to a layer of extracellular matrix [15,16]. The SCS is permeable to small soluble antigens (i.e. molecules with a dynamic radius of less than ~5.5 nm, corresponding to a molecular mass of less than ~70 kDa) [17], but not to larger particulate antigens (like intact viruses). Indeed, it has been shown that ~200 nm-sized structures such as synthetic microspheres or viral particles are captured and retained by SCS macrophages, which secondarily translocate these particulate antigens across the SCS floor and display them to underlying follicular B cells [11,12,13**]. Unlike non-cognate B cells, antigen-specific follicular B cells make prolonged contacts with SCS macrophages, acquire antigen, up-regulate CC-chemokine receptor 7 (CCR7) and the G protein-coupled receptor EBI2, and migrate to the B cell-T cell boundary where they recruit CD4⁺ T cell help necessary for maximal activation [9,14**,18–23]. The importance of

SCS macrophage-mediated antigen retention for follicular B cell activation is highlighted by the observation that disruption of the SCS macrophage lining occurring during infection or inflammation impairs B cell responses to subsequent viral infection [24^{••}]. Following activation at the B cell-T cell boundary, B cells undergo vigorous proliferation in the outer B cell follicle. Within a few days after antigen encounter, while some B cells differentiate into plasmablasts and accumulate at extrafollicular sites, others re-enter B cell follicles and give rise to germinal centers [25]. An interesting research question pertains to the spatiotemporal dynamics of B cell activation in response to viruses that fail to induce early neutralizing antibody responses (e.g. lymphocytic choriomeningitis virus [LCMV] in mice or hepatitis B virus [HBV], hepatitis C virus [HCV] or human immunodeficiency virus [HIV] in humans). It was recently shown that, upon LCMV infection, virus-specific B cells move to the interfollicular and T cell area of the draining lymph node, where they engage in prolonged interactions with a population of CD11b⁺Ly6C^{hi} inflammatory monocytes that is recruited in a type I interferon (IFN-I)-dependent and CCR2-dependent fashion [14^{••}]. Inflammatory monocytes induce B cell apoptosis via nitric oxide and, indeed, experimental ablation of inflammatory monocytes or inhibition of their lymph node recruitment leads to increased survival of antiviral B cells and recovery of protective antibodies [14^{••}]. Future studies should assess the relative capacity of different viruses to induce the lymph node recruitment of inflammatory monocytes and the role these cells might play in suppressing antibody responses to those infections. Recent studies have suggested that virus-induced type I interferon is not only required for the lymph node recruitment of inflammatory monocytes, but it also promotes the expansion and differentiation of virus-specific effector CD8⁺ T cells that kill antiviral B cells [26^{••}] and it indirectly stimulates the differentiation of antiviral B cells into short-lived plasma cells [27^{••}]. The detailed characterization of the molecular mechanisms whereby type I interferon hinders antiviral B cell responses might lead to novel therapy for chronic infectious diseases as well as more rational vaccination strategies.

Priming of antiviral T cells

Although subcapsular sinus macrophages play a key role in early B cell activation, they do not seem to be involved in direct priming of antiviral T cells [4]. Local infection with vaccinia virus, however, induces inflammasome activation in subcapsular sinus macrophages, which is immediately followed by cell death and release of extracellular apoptosis-associated speck-like protein with a CARD domain (ASC) specks [28]. This short-lived inflammasome signaling causes a vigorous lymph node recruitment of T cells and inflammatory cells from the circulation, ultimately increasing the magnitude of the T cell response [28].

Intravital microscopy studies have revealed distinct spatiotemporal dynamics of CD4⁺ and CD8⁺ T cell activation upon viral infections [29^{••},30,31,32^{••}] (Figure 1). The initial activation of CD4⁺ and CD8⁺ T cells was shown to be spatially and temporally separated, involving different dendritic cell subsets and varying between viruses and infection routes [31,32^{••}] (Figure 1). For instance, upon subcutaneous vaccinia virus infection, naïve CD8⁺ T cells are initially primed by infected DCs near the SCS [29^{••},30,31], whereas naïve CD4⁺ T cells get activated deeper in the T cell zone by different non-infected DCs [31] (Figure 1). Using a cutaneous herpes simplex virus infection model (where no infected cells are found within secondary lymphoid organs), instead, it was shown that early priming of CD4⁺ T cells involved clustering with migratory skin DCs in the T cell area (Figure 1). By contrast, priming of naïve CD8⁺ T cells was delayed and did not involve migratory DCs but rather lymph-node resident XCR1⁺ DCs [32^{••}] (Figure 1). At later stages of infection in both experimental systems, XCR1⁺ DCs present antigen to both CD4⁺ and CD8⁺ T cells [31,32^{••}] (Figure 1). These XCR1⁺ DCs are the critical platform involved in CD4⁺ T cell augmentation of CD8⁺ T cell responses [31] (Figure 1). Moreover, plasmacytoid dendritic cells (pDCs) were shown to support XCR1⁺ DC maturation and cross-presentation, therefore indirectly optimizing CD8⁺ T cell priming [33] (Figure 1). Indeed, it was found that initial activation of CD8⁺ T cells by conventional DCs leads to production of CCL3 and CCL4 as well as XCL1 chemokines which attract pDCs and XCR1⁺ DCs, respectively [33] (Figure 1). The simultaneous presence of pDCs, XCR1⁺ DCs and CD8⁺ T cells within the same tissue niche allows for pDC-derived type I interferon to optimize the maturation and cross-presentation of XCR1⁺ DCs, thus enhancing the developing CD8⁺ T cell response [33] (Figure 1).

Whereas the spatiotemporal dynamics of antiviral CD8⁺ T cell priming are beginning to unravel, less is known about the dynamics of CD4⁺ T cells upon viral infection. For instance, we currently have a poor understanding of the spatiotemporal dynamics whereby CD4⁺ T cells differentiate into distinct T helper cell subsets (e.g. Th1, TFh, Th17, etc.) upon the same or different types of viral infections.

Secondary lymphoid organs also serve as sites for reactivation of central memory T cells upon secondary viral infection. Two studies have recently analyzed the lymph node localization and dynamic behavior of central memory CD8⁺ T cells upon viral infection [34,35[•]]. Both studies reported that, upon peripheral infection, CXCL9 recruits central memory CD8⁺ T cells from the cortical ridge to the subcapsular sinus and IFN- γ derived from activated memory T cells activates a feed-forward circuit that enhances CXCL9 expression by both stromal cells and macrophages in the subcapsular sinus [34,35[•]]. This

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