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Tuning B cell responses to antigens by cell polarity and membrane trafficking

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ABSTRACT

The capacity of B lymphocytes to produce specific antibodies, particularly broadly neutralizing antibodies that provide immunity to viral pathogens has positioned them as valuable therapeutic targets for immunomodulation. To become competent as antibody secreting cells, B cells undergo a series of activation steps, which are triggered by the recognition of antigens frequently displayed on the surface of other presenting cells. Such antigens elicit the formation of an immune synapse (IS), where local cytoskeleton rearrangements coupled to mechanical forces and membrane trafficking orchestrate the extraction and processing of antigens in B cells. In this review, we discuss the molecular mechanisms that regulate polarized membrane trafficking and mechanical properties of the immune synapse, as well as the potential extracellular cues from the environment, which may impact the ability of B cells to sense and acquire antigens at the immune synapse. An integrated view of the diverse cellular mechanisms that shape the immune synapse will provide a better understanding on how B cells are efficiently activated.

1. Introduction

B lymphocytes are key elements of adaptive immunity as they mount antibody responses upon recognition of foreign antigens and display important roles as antigen-presenting cells that shape immune reactions. To achieve complete activation, B cells rely on their capacity to capture external antigens and present them as peptide fragments loaded onto major histocompatibility complex class II(MHC II) molecules to CD4 + T cells. This interaction, known as T–B cooperation, allows B cells to differentiate into high-affinity antibody-producing plasma cells and to develop into memory B cell populations (Mitchison, 2004). Here, we describe how B cells acquire antigens by establishing immunological synapses with antigen-presenting cells and review recent progress made on key regulatory aspects involved in synapse assembly and modes of antigen extraction. Special emphasis will be given on how B cells coordinate proteolytic and mechanical extraction of immobilized antigens and how external cues can impact the intracellular mechanisms involved. Understanding how B cells coordinate polarized membrane trafficking with local mechanical forces to efficiently acquire and present extracellular antigens can help unravel how humoral responses are tuned in physiological and pathological settings.

2. Mechanisms used by B cells to acquire surface-tethered antigens

It is widely accepted that in vivo, B cells encounter antigens immobilized on the surface of presenting cells (Carrasco and Batista, 2007; Batista and Harwood, 2009; Suzuki et al., 2009). Thus, the current view on how B cells acquire antigens has rapidly shifted from classical receptor-mediated endocytosis of soluble ligands towards the formation of a transient polarized cellular domain, the immune synapse, where both signaling cascades are organized and antigen uptake takes place (Harwood and Batista, 2008);(Yuseff et al., 2009; Pierce and Liu, 2010). Immune synapse formation is initiated upon recognition of surface-tethered antigens by the B cell receptor (BCR), triggering a rapid actin–dependent membrane spreading response (Fleire et al., 2006), where antigen-BCR complexes are gathered into micro-clusters that contain signaling molecules, such as src family tyrosine kinases, Lck/Yes novel tyrosine kinase (Lyn) and Spleen tyrosine kinase (Syk) (Depoil et al., 2009; Pierce and Liu, 2010). Membrane spreading is followed by a contraction phase in which antigen-BCR complexes are transported into a central cluster by the concerted action of the microtubule motor Dynein and actin cytoskeleton rearrangements (Fleire et al., 2006; Schnyder et al., 2011). BCR downstream effectors involved actin rearrangements include the small GTPases Rac1 and Rac2 (Brezski

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and Monroe, 2007; Arana et al., 2008), molecules from the ERM-family (Treanor et al., 2011) and the Rap1-cofilin-1 pathway, which coordinates both actin and microtubule organization at the immune synapse (Wang et al., 2017). Ultimately, a mature immune synapse is formed where receptors and signaling molecules are segregated into defined domains of the synaptic membrane and organized into concentric regions. The central region, termed central-supra-molecular activation cluster (cSMAC), contains signaling molecules and antigen-engaged BCRs whereas the peripheral and distal SMACs (pSMAC and dSMAC) are enriched in adhesion molecules such as the Lymphocyte function-associated antigen 1(LFA-1) and filamentous actin (F-actin), respectively(Batista et al., 2001).Antigens concentrated at the center of the immune synapse are extracted and internalized into specialized endo-lysosome compartments, where they undergo proteolytic processing. The peptides generated by this process are loaded onto MHC II molecules and exported to the surface for presentation to CD4 + T cells. Thus, antigen presentation by B cells ultimately relies on their capacity to efficiently extract antigens at the immune synapse. As described below, this process is regulated by environmental cues, which can originate from co-stimulatory factors as well as from the physical context in which antigens are presented to B cells.

Initial observations made by Batista and Neuberger (Batista and Neuberger, 2000; Batista et al., 2001) described how B cells extracted antigens and associated membranes from the surface of presenting cells. Since then, two non-exclusive mechanisms that explain the molecular basis of this process have emerged (Fig. 1). The first one involves the local secretion of lysosomes that release proteases and acidify the synaptic cleft where antigen is encountered, facilitating its extraction (Yuseff et al., 2011). The second one proposes that myosin IIA-mediated pulling forces exerted at the synaptic membrane trigger the invagination of antigen-containing membranes, which are subsequently internalized into clathrin-coated pits (Natkanski et al., 2013). Clathrin-mediated endocytosis seems to be the prevalent mechanism used by B cells to uptake either soluble or membrane-tethered antigens, which is highlighted by the fact that depletion of clathrin, its adaptor, AP2, or mutations in AP2 recognition motifs within the BCR, strongly impair the endocytosis of both types of antigens, (Busman-Sahay et al., 2013; Natkanski et al., 2013).However, coalescence of lipid microdomains could also control BCR internalization at the immune synapse by organizing signaling cascades that modulate clathrin- mediated uptake (Stoddart et al., 2002).

Intriguingly, the two major functions associated to BCR engagement, endocytosis and signaling, seem to be mutually exclusive events, where BCR endocytosis via clathrin coated pits was shown to be restricted to non-signaling BCR molecules(Caballero et al., 2006). Given that BCR-engaged antigens coalesce at the center of the immune synapse, it would be of interest to determine whether endocytosis of the BCR occurs specifically within this region and whether dephosphorylation of the receptor occurs prior to this process.

Interestingly, the mode of antigen extraction used by B cells depends on the physical properties of their environment: antigens presented on flexible surfaces are mechanically internalized whereas antigens presented on rigid surfaces are acquired by proteolytic extraction (Spillane and Tolar, 2017).Until now, the evidence put forward suggests that both modes of antigen extraction are not used cooperatively by B cells, which rather rely on one mechanism, determined by the rigidity of the surface in which the antigen is recognized (Spillane and Tolar, 2017).This is supported by evidence showing that B cells exerting mechanical extraction of surface-tethered antigens, no longer recruit lysosomes to the synaptic membrane. Nevertheless, it is unknown whether lysosomes are transported to sites of membrane invaginations generated by pulling forces or whether impaired lysosome recruitment and secretion have an impact on mechanical forces employed by B cells to extract antigens at the immune synapse. Intriguingly, Myosin II regulates the convergence of MHC class II and B Cell Receptor-containing antigen (BCR-Ag) complexes into lysosomes devoted to Ag processing (Vascotto et al., 2007), suggesting that an interplay between mechanical and chemical extraction of antigens indeed exits. However, further studies are required elucidate the potential crosstalk between both mechanisms. Interestingly, the mode of antigen extraction by B cells was also shown to vary within different subsets of their lineage. Whereas naive and memory B cells accumulate antigen at the center of the immune synapse, germinal center (GC) B cells gather antigen within small microclusters, which are pushed towards the synapse periphery where extraction occurs predominantly through mechanical forces linked to local actin cytoskeleton dynamics (Nowosad et al., 2016). Indeed, such a mechanism was suggested to enable B cells to extract antigen with better affinity discrimination, thereby improving the

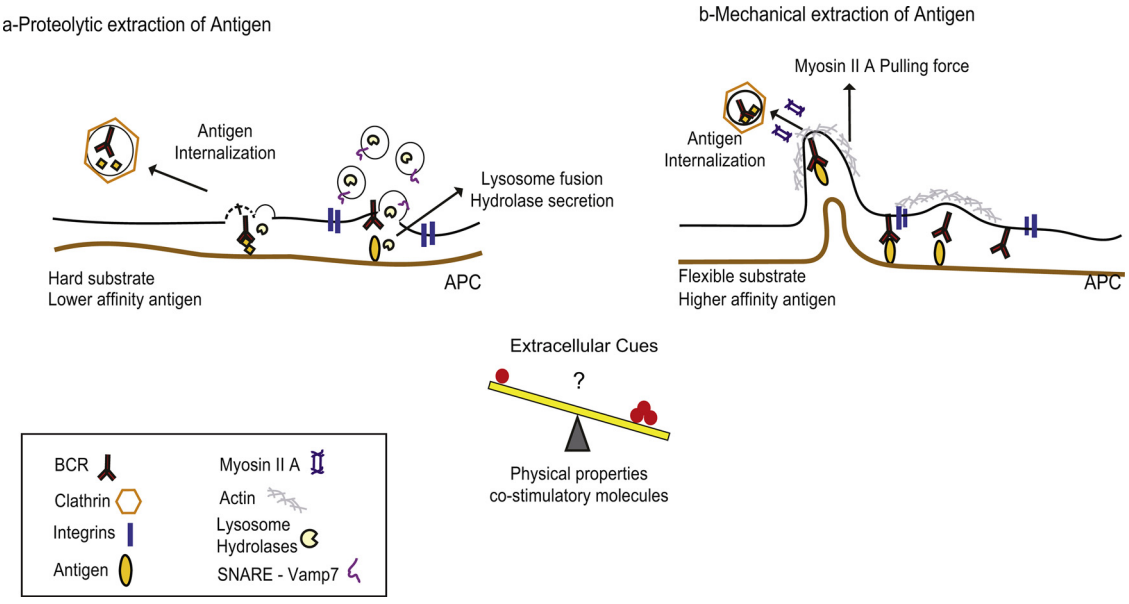

Fig. 1. B lymphocytes use different mechanisms to acquire surface-tethered antigens. (**a**) Vamp-7 dependent local fusion of lysosomes leads to the secretion of hydrolases at the synaptic membrane, which promotes antigen extraction. (**b**) Myosin II-dependent forces deform the synaptic membrane to pull out tethered antigens. The use of each mechanism relies on the physical properties of the surface in which antigens are presented to B cells, however the role of extracellular cues, including ligands from the extracellular matrix remains to be determined.