Antigen tethering proteins on follicular dendritic cells influence the affinity and diversity of germinal-center B cells

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To protect a host, the adaptive immune system must ideally generate antibodies that bind the pathogen with high affinity, yet are diverse enough to protect against potential escape mutations. During an immune response, novel antibodies are generated in microanatomical environments called germinal centers (GCs), in which B cells undergo rounds of proliferation, somatic hypermutation, and selection. Here, we present a biophysical mechanism by which the properties of the tethering proteins on the surface of follicular dendritic cells (FDCs), which present antigen to B cells, may influence the degree of diversity and affinity of the GC output. FDCs tether antigen via two classes of receptors: complement receptors (CRs, namely CR1 and CR2) and an Fcγ receptor (FcγR, specifically FcγRIIB). Using minimal models, we suggest that high expression of FcγR helps increase the affinity of dominant B-cell lineages, whereas low expression encourages epitope diversity of the B-cell repertoire. Our model is consistent with experimental observations reporting low affinity but high diversity in absence of FcγRs on FDCs. We comment on connections to other proposed roles for the FDC-expressed FcγRs, whose functions remain an area of investigation.

One of the key protective features of the adaptive immune system is the generation of novel antibodies (Abs). Mechanistically, the process of affinity maturation occurs in microanatomical environments known as germinal centers (GCs) [1, 2] (Fig. 1a). GCs are organized into two compartments, the Dark Zone (DZ) and the Light Zone (LZ), which are responsible for diversity generation and selection, respectively. In the LZ, antigen (Ag) is presented on the surface of follicular dendritic cells (FDCs) [3–5], and B cells explore the follicles for cognate Ag. Upon detection, a B cell attempts to extract Ag using its B-cell receptor (BCR) [6–13]. If extracted, the Ag is endocytosed, degraded into peptides, and presented on MHC class II to follicular helper T cells (T_{FH}). If sufficient T-cell help is received, the B cell migrates to the DZ, where it undergoes rapid division and somatic hypermutation. The number of divisions is set by the quality of the T-cell help [14]. The mutated daughters then return to the LZ and repeat this process. Crucially, GC B cells will undergo apoptosis if they fail to either find cognate Ag or receive T-cell help. Hence, B cells that are able to acquire more Ag and therefore receive more T-cell help will produce more progeny and thus form a larger fraction of the future GC population. During this process, a small fraction of B cells are exported to plasma or memory cell fates.

A key requirement for a functional GC reaction is that B cells expressing BCRs with higher affinity for Ag on average acquire more Ag from the surface of FDCs. Put simply, if Ag is bound too tightly to the FDC, then none of the B cells will be able to extract the Ag and the GC reaction will fail. Conversely, if Ag is only weakly adhered to the FDC, then all cognate B cells will be equally able to extract Ag, and no discrimination on the basis of affinity will take place. Given that each Ag is distinct and that the naïve BCR repertoire is the result of random VDJ recombination, how this system robustly calibrates itself remains an open question.

This problem is made particularly rich because in natural settings, different BCRs may bind to different epitopes (binding sites) on the target Ag. A second source of complexity is the role of Ab feedback [15–22]. As shown in Fig. 1b, Ag is often presented on the membrane of an FDC in the form an immune complex (IC), consisting of an Ag or Ags coated in complement (proteins of the innate immune system) and Abs. These IC Abs were either present in the naïve repertoire, produced earlier in the immune response, or, in experimental or clinical settings, introduced exogenously (e.g., in Ab therapy). These IC Abs are expected to affect the dynamics of the GC reaction, for instance by blocking BCRs that compete for the same or overlapping epitopes. In different contexts, such so-called "epitope masking" has been proposed both to drive GC selection to higher affinity (by incrementally increasing the difficulty of BCRs to bind to Ag [15]) or to drive diversification of GCs (by giving a competitive edge to B cells cognate to alternative epitopes [18]).

Here we provide a biophysical analysis of how the proteins that tether ICs to the FDC may influence tradeoffs between affinity and diversity during GC selection. Our study focuses on the notable feature that ICs are bound to FDCs via two types of surface proteins: The complement receptors (CRs) are relatively high-affinity receptors ($K_A \sim 10^8 - 10^9$ M^{-1}) that bind to ICs via complement fragments, which may themselves be cova-

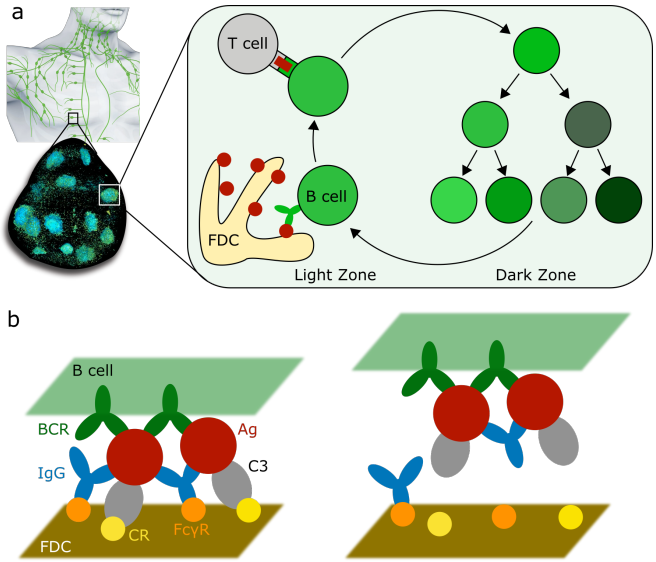

FIG. 1. **The germinal center reaction and extraction of immune complexes.** (a) Left: schematic of the human lymphatic system with a zoom-in confocal microscopy image of a single lymph node (adapted from [23]). Individual GCs are labeled by expression of activation-induced cytidine deaminase (AID). Right: basic steps of a GC reaction include the B cell extracting Ag (red) with its BCR from the surface of an FDC, presenting pMHC to a T_{FH}, then migrating to the DZ to undergo proliferation and somatic hypermutation (represented by color change). (b) Schematic of the B cell-FDC interface. The IC consists of Ag (red), Abs (e.g. IgG, blue) and complement proteins (e.g. C3, gray). The B cell binds directly to the Ag (red) via its BCR (green). The FDC binds to the IC via the complement (yellow) and FcγRs (orange). The B cell attempts to extract Ag by physically retracting its cell membrane. (Schematic of lymphic system in (a) adapted from Stocktreck Images)

lently bound to Ags [24, 25]. CRs are known to play a role in the spatial organization of GCs, and are often thought to be the primary receptor for long-term retention of Ag [26]. The second receptor is FcγR (specifically FcγRIIB), which binds to ICs via the conserved tail of IgG Abs [27–31]. Curiously, FcγR is a relatively low-affinity receptor ($K_A \sim 10^4 - 10^7$ M^{-1}) [32], which has caused its potential mechanical functions to be underexplored. However, we argue that in the context of oligomeric or polymeric ICs, the multivalent binding of many weak FcγRs can have a substantial effect. Using minimal models, we arrive at the following potential implications for affinity maturation: without FcγR, our analysis suggests that epitope masking would limit affinity maturation and instead promote diversification for Ags with multiple epitopes. By contrast, if FcγR is highly expressed on the FDC, the composite IgG-FcγR bonds create an extraction threshold that is felt equally by all B cells regardless of epitope specificity. This egalitarian, moving threshold reduces Ag extraction by lower affinity B cells that target alternative epitopes, and thereby protects the dominant, high affinity B-cell lineages against competition.

Results

Without FcγR, epitope masking promotes epitope diversity and stalls affinity maturation. To motivate the role of FDC FcγRs, we first examine B cell competition when FcγR is absent. First consider the simplest situation in which the Ag has only one epitope, as shown in Fig. 2a. Using a simple model for Ag extraction based on binding and unbinding rates of the relevant noncovalent bonds, one finds that the probability that the B cell successfully extracts this Ag is

$$P_{\text{primary}} = \left(\frac{1}{1+\tau_{\text{IgG}}/\tau_{\text{BCR}}}\right)\left(\frac{1}{1+\tau_{\text{CR}}/\tau_{\text{BCR}}}\right), \quad (1)$$

where τ_{IgG} is the average IgG-Ag bond lifetime, τ_{CR} is the CR-complement bond lifetime, and τ_{BCR} is the BCR-IgG bond lifetime. A contour plot of Eq. (1) is shown in Fig. 2b, with contours at 5%, 50%, and 95% probability of extracting the Ag. The salient feature is as follows: when the IgG is fairly weak, the main competition for Ag extraction is between the BCR and the CR; however, when the IgG is stronger than the CR, the main barrier to Ag extraction is whether or not the BCR is bound to the Ag in the first place. This model is admittedly based on a highly simplified picture of Ag extraction (see Discussion); yet, the qualitatively important feature is the presence of this elbow, which will be present in any epitope masking model because there must be a crossover between the relative difficulty for the BCR to overcome tethering and masking.

The solid red curve in Fig. 2b shows the typical immunological trajectory in the space of IgG and BCR affinity for the dominant lineage. Initially, the IC IgG is very weak, but the BCR and IgG affinity progressively increase throughout the immune response. Similarly, Fig. 2c shows the B-cell lineage population and affinity as functions of time. Notably, the affinity (expressed in terms of τ_{BCR}) increases indefinitely. This happens because in the presence of a single epitope, epitope masking continuously challenges B cells to create higher and higher affinity receptors to bind to the Ag. This is consistent with the interpretation offered in Ref. [15], which suggests an effective comoving equilibrium between soluble IgG and GC BCR affinity.

However, the implications of masking are more subtle if the Ag has additional epitopes, as shown in Fig. 2c for two epitopes. In the limit that the IgG for the primary epitope does not block binding to the second epitope, the extraction probability for the secondary lineage will be:

$$P_{\text{secondary}} = \frac{1}{1+\tau_{\text{CR}}/\tau_{\text{BCR}}}, \quad (2)$$

which is independent of the IgG produced by the primary epitope. As shown in Fig. 2e, once the IgG produced by

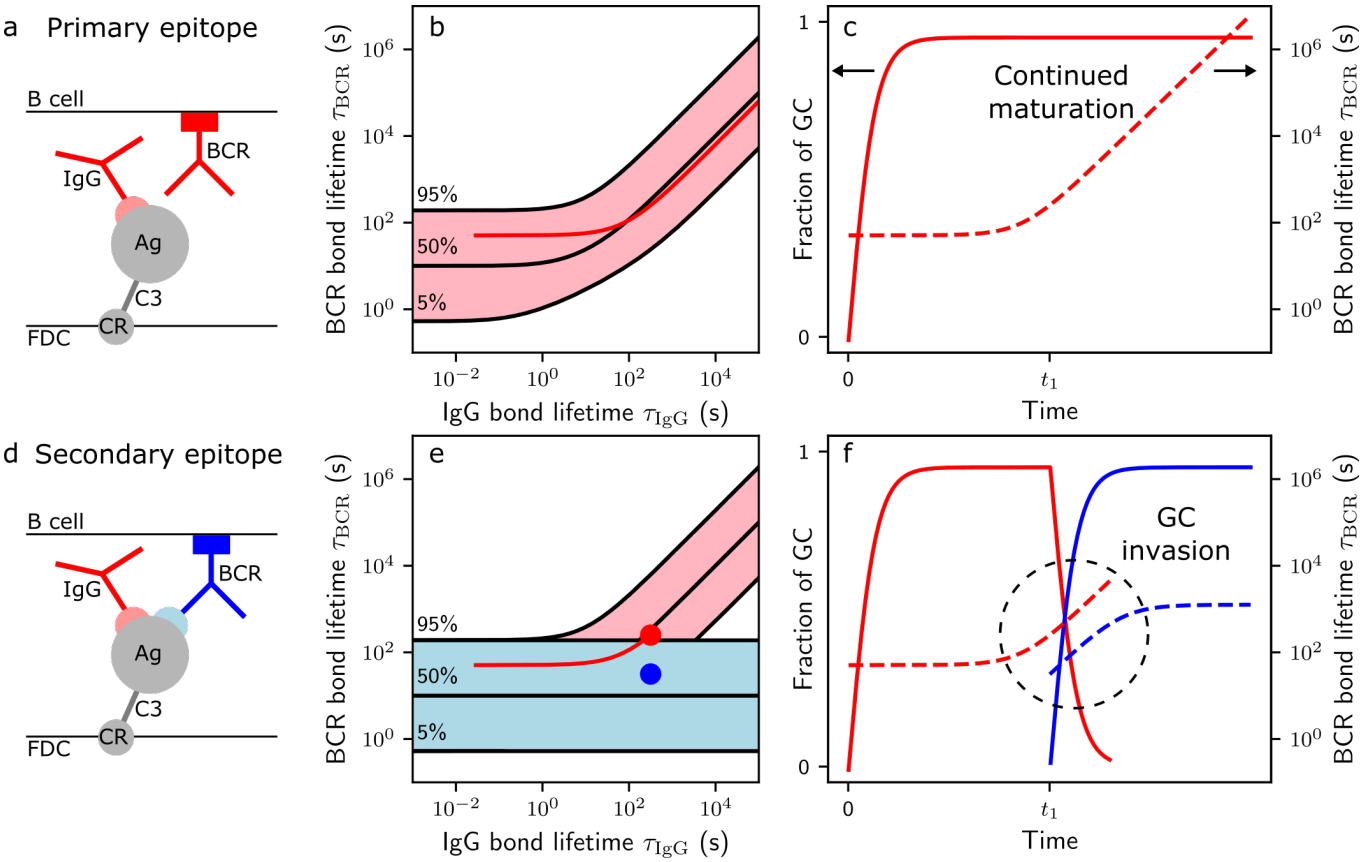

FIG. 2. **Epitope masking on multi-epitope antigens limits affinity maturation.** (a) Junction between a B cell and an FDC lacking FcγR. In this panel, the Ag only has single epitope (red). The competition between the BCR and the floating IgG for the same epitope reduces the probability of the BCR to bind. (b) Contour plot (level curves at 5%, 50%, and 95%) of the probability of the B cell to extract an Ag, see Eq. (1). The light red filling indicates the region where the gradient is strongest, enabling hill climbing. The solid red curve indicates the bond lifetime of the dominant IgG and of the BCR from the dominant B-cell lineage as parameterized by time. (c) Time trace of the fraction of the population comprising the dominant B-cell lineage (solid line), along with the affinity of that lineage, expressed in terms of bond lifetime. (d) Schematic of the B cell-FDC interface when the Ag has a second, independent epitope. (e) Extraction probability landscape for a BCR specific for the primary (red) and secondary (blue) epitope is plotted as a function of the bond lifetime of the IgG specific for the primary epitope, see Eq. (2). The highlighted red and blue points indicate that a secondary lineage (blue), with lower affinity for Ag, can have a higher probability than the primary lineage (red), whose ability to extract Ag is limited by epitope masking. (f) Resulting time trace of the population fraction (solid) and epitope affinity (dashed) of the dominant (red) and secondary (blue) B-cell lineages. The secondary lineage, arriving at time t_1, can acquire the Ag more effectively than the existing dominant lineage due to epitope masking.

the primary lineage exceeds the strength of the CR, the following situation arises: the secondary lineage (blue) can have a weaker affinity than primary (red), but because the primary (red) has to compete with its own IgG, the primary lineage has a lower probability of extracting Ag. Thus, the secondary lineage (blue), will outcompete the primary lineage, despite having lower affinity (see Fig. 2f). Consequently epitope masking stalls affinity maturation and instead drives epitope diversification.

FcγR enables continued affinity maturation. To enable continued affinity maturation in the typical case when Ags possess multiple epitopes, a mechanism is required such that both the primary and secondary lineages experience an increasing barrier to extracting Ag as the ambient IgG affinity increases. We propose that expression of the FcγR on the FDC may provide such a mechanism. At first glance, it may seem counterintuitive that FcγR could play any role at all in the mechanics of extraction—its affinity for Fcγ ($10^4 - 10^7$ M^{-1}) is orders of magnitude smaller than CR1 or 2 for complement ($10^8 - 10^9$ M^{-1}) [25, 32]. Yet, a closer biophysical examination suggests that the effect can be quite dramatic. Consider the case shown schematically in Fig. 3a,d where an Ag is bound to an FDC by both a CR and an FcγR bond. For the B cell to extract the Ag from the FDC, both the CR bond and the Fcγ bond must simultaneously break. However, at relevant temperatures, the bonds will reform on a timescale $\tau_{\rm off}$ that is much shorter than either the

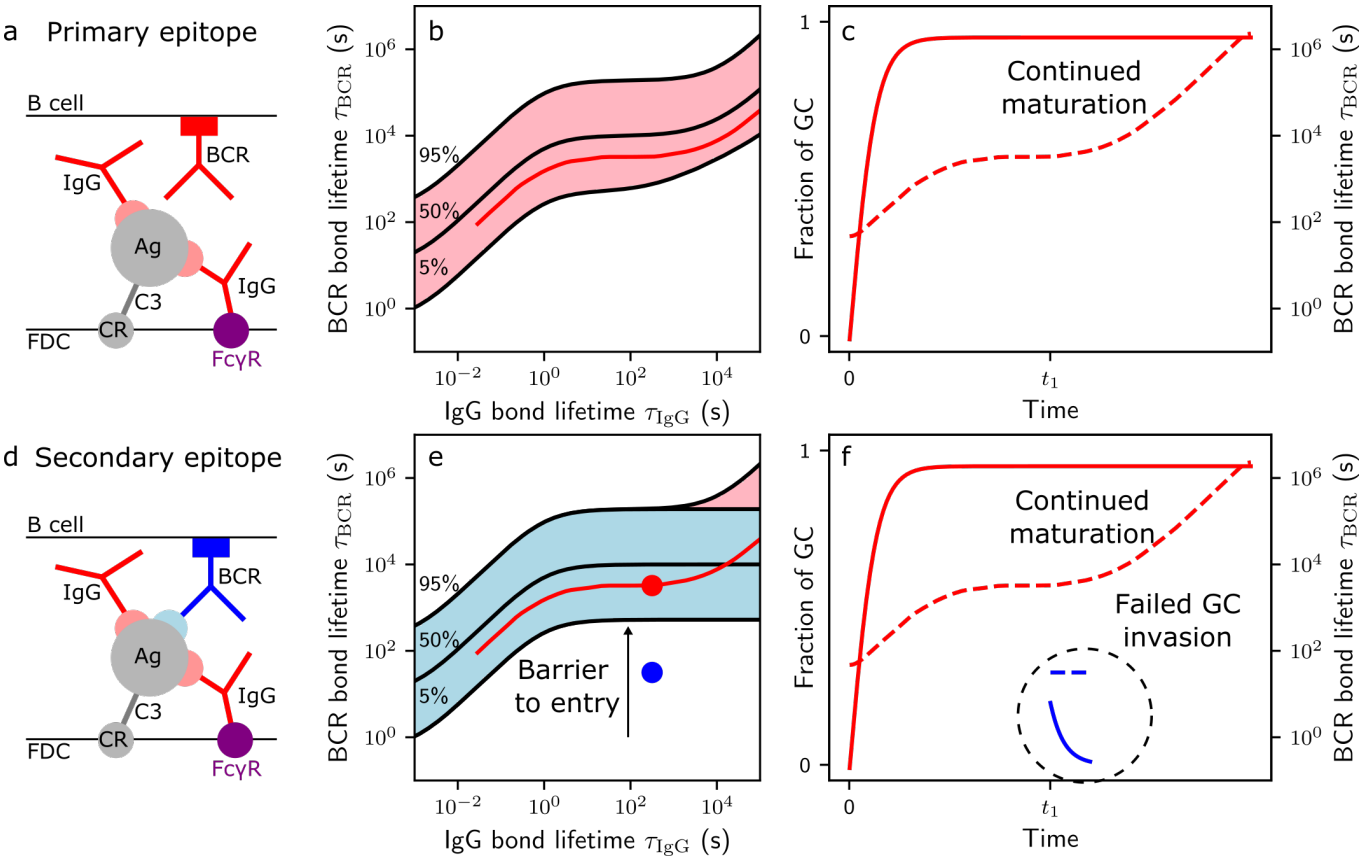

FIG. 3. **The FcγR on the FDC protects affinity maturation of dominant B-cell lineages.** (a) Schematic of an IC anchored to an FDC via both a CR-CR3 and an IgG-FcγR bond. (b) Contour map of the resulting probability of Ag extraction, *cf.* Fig. 2b. (c) Time trace of a single lineage in the presence of a single epitope. (d) Schematic as in panel (a), but now with a secondary epitope. (e) Extraction probability landscapes for the primary (red) and secondary (blue) epitopes. Unlike Fig. 2e, both the landscapes for the primary and secondary epitopes experience an increasing ramp with the primary IgG bond lifetime. This limits the ability of low-affinity B cells targeting alternative epitopes to compete in the GC, thereby protecting B cells cognate to primary epitopes from competition. (f) Time trace of the population dynamics showing the failure of a secondary B-cell lineage to compete in the GC.

CR lifetime τ_{CR} or the FcγR lifetime $\tau_{Fc\gamma R}$. Hence, the redundancy of having a second bond, even if weak, dramatically decreases the rate of detachment, because the chance of simultaneous breakage is rare.

For a concrete illustration, consider the minimal ICs in Fig. 3a,d. Using typical binding and unbinding rates, the probability of Ag extraction by the secondary lineage is

$$P_{\text{secondary,Fc}\gamma\text{R}} = \frac{1}{1+\tau_*/\tau_{\text{BCR}}}, \tag{3}$$

where

$$\tau_* = \tau_{\text{CR}} \frac{1+\tau_{\text{IgG}}/\tau_{\text{off}}}{1+\tau_{\text{IgG}}/\tau_{\text{Fc}\gamma\text{R}}}, \tag{4}$$

and $\tau_{Fc\gamma R}$ is the average bond lifetime of the FcγR bond. And for the primary lineage, there is an additional factor associated with masking:

$$P_{\text{primary,Fc}\gamma\text{R}} = \left(\frac{1}{1+\tau_{\text{IgG}}/\tau_{\text{BCR}}}\right) P_{\text{secondary,Fc}\gamma\text{R}}. \tag{5}$$

The two landscapes in Eqs. (3,5) are shown in Figs. 1e,b, respectively. The key qualitative feature is that the FcγR bond increases the extraction threshold for both the primary and secondary lineage of B cells. This increase is felt by both lineages because the FcγR, unlike masking, does not affect the ability of a specific BCR to bind to the Ag, but rather affects the way the Ag binds to the FDC. Interestingly, if only a single epitope is present, the effect of FcγR on the affinity maturation dynamics is qualitatively unnoticeable: the single B-cell lineage increases affinity monotonically in Fig. 3c, just as in Fig. 2c. However, when a second epitope is available, FcγR has a dramatic qualitative effect: BCRs with weak affinity to secondary epitopes are no longer able to extract Ag and compete (see Fig. 3e). The invasion is avoided be-

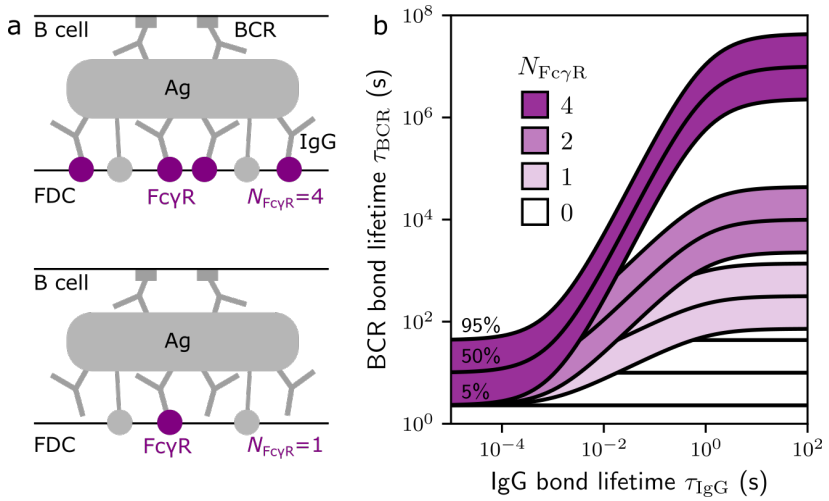

FIG. 4. **FcγR expression steers competition landscape of GC B cells.** (a) Schematics of FDCs with high ($N_{\mathrm{Fc\gamma R}} = 4$) and low ($N_{\mathrm{Fc\gamma R}} = 1$) expression of FcγR. (b) Ag-extraction probability landscape as a function of the number of FcγR bonds, see Eq. (6).

cause the extraction probability landscape comoves for both the primary and secondary epitope. This analysis suggests that FcγR may act to suppress epitope diversification and allow primary lineages to continue affinity maturation.

Cells often regulate receptor expression to control behavior. This raises the question of how the number of receptors bonded to an IC influence the probability of extraction by a B cell. Consider the IC in Fig. 4a, which is bound to the B cell by N_{BCR} BCRs, and to the FDC through N_{CR} CRs and $N_{\mathrm{Fc\gamma R}}$ FcγRs. In the limit that $\tau_{\mathrm{off}} \ll \tau_{\mathrm{Fc\gamma R}}, \tau_{\mathrm{CR}}$, the probability that a given B cell extracts an Ag is given by:

$$P_{\mathrm{extract}} = \frac{1}{1 + (\tau_*/\tau_{\mathrm{BCR}})^{N_{\mathrm{BCR}}}}, \tag{6}$$

which is a Hill function with crossover τ_* and cooperativity N_{BCR}. The crossover τ_* depends on the number and type of the receptors bound to the FDC, as well as the affinity of the IgG:

$$\tau_* \approx \tau_{\mathrm{off}} \left(\frac{\tau_{\mathrm{CR}}}{\tau_{\mathrm{off}}}\right)^{\frac{N_{\mathrm{CR}}}{N_{\mathrm{BCR}}}} \left(\frac{1 + \tau_{\mathrm{IgG}}/\tau_{\mathrm{off}}}{1 + \tau_{\mathrm{IgG}}/\tau_{\mathrm{Fc\gamma R}}}\right)^{\frac{N_{\mathrm{Fc\gamma R}}}{N_{\mathrm{BCR}}}}. \tag{7}$$

As illustrated by the exponents in Eq. (7), the numbers of bonds of each type between each cell membrane exponentially alters the value of the τ_{BCR} required to extract Ag.

Fig. 4b illustrates the probability of Ag extraction for different numbers of FcγR bonds. A larger number of FcγR bonds makes it more difficult for low-affinity B cells (targeting any epitope) to extract Ag. This prevents low-affinity B cells that target alternative epitopes from outcompeting higher-affinity B cells that target the primary epitope and therefore face the obstacle of masking. A smaller number of FcγR bonds may impose negligible Ag-extraction barriers for B cells targeting alternative epitopes, allowing them to compete in and potentially take over the GC. Because the FDC can regulate the expression of FcγR, this raises an intriguing possibility that FDCs may actively influence resulting affinity and epitope diversity of the GC (see Discussion).

Discussion

In brief, we propose a biophysical picture in which the two Ag tethering proteins on the FDC collaborate to regulate the B-cell epitope diversity generated by the GC reaction. A key prediction of this model is that the absence of FcγR on the FDC, GCs should generate relatively low affinity but highly diverse B-cell repertoires. This is consistent with experiments [33] in which mice lacking FcγRs on FDCs show reduced affinity but increased diversity. Interestingly, the magnitude of the effect in these experiments was Ag-dependent. Based on our results, additional investigation into the Ab and complement valency of the Ags would be informative. For instance, the difference between mice with and without FcγR should be amplified for Ags with a propensity to form large ICs.

These knockout experiments could be complemented by additional probes. For instance, consider immunization with an Ag featuring two well-separated epitopes, A and B. In scenario 1, assume that IgG with high-affinity for epitope A is administered before and during immunization. In this case, FcγR bonds will suppress the immune response for both epitope A and B. In scenario 2, instead of administering IgG, suppose we administer $(\mathrm{Fab})_2$ which lacks an Fcγ tail. In this case, our mechanism would imply that development of Abs for epitope A may be suppressed due to masking by the external $(\mathrm{Fab})_2$, but proper affinity maturation for epitope

B should proceed. Versions of this experiment could also be done with other non-IgG immunoglobulins.

In addition to their mechanical roles in Ag extraction, other functional roles for CRs and FcγRs on FDCs have been demonstrated or proposed. The expression level of CRs on FDCs is relatively constant over time, and these receptors have been implicated in defining the spatial organization of the LZ [26], retaining Ag for long periods of time [4], and receiving Ag from noncognate B-cell escorts [34]. The precise role of FcγR is a subject of debate. FcγR is also expressed by GC B cells and has an inhibitory effect. It has been suggested that one role of the FcγR on FDCs is to sequester Fc tails away from the B cell, thereby making ICs on the surface of FDCs more immunopotent [30]. Moreover, FcγR expressed on FDCs appears to have an activating effect, including chemokyne release and further upregulation of FcγR [31].

The sensitivity of Ag-extraction probability to FcγR expression, *cf.* Eq. (7) and Fig. 4, suggests an intriguing possibility: FDCs could actively regulate the affinity-diversity trade-off over time. Unlike the CRs, whose expression is roughly constant over time, FcγR is upgregulated roughly 50-fold upon FDC activation [30]. Does this early upregulation initially focus the GC reaction on nurturing one immunodominant clone? A later putative downregulation could then allow epitope diversification on longer time scales. A crossover from affinity increase early in the GC reaction to increased diversity later is indeed generally observed; however, any connection to temporal modulation of FcγR expression on FDCs has not been systematically studied, to our knowledge. Such an effect would need to be disentangled from several other factors influencing B-cell selection, such as evolving follicular helper and regulatory T cell populations [35–37], changes in Ag levels [38], and circulating memory B cells [39].

One can envision further elaborations to the simplified biophysical model we present. When extracting Ag, GC B cells form a specialized immunological synapse in which they exert pico-Newtons of force on localized contacts. It has been proposed, for example, that the amount of force applied is tuned to optimize affinity discrimination [12]. Additional features worth investigating are that complement can bind to Abs in addition to Ag, the polymeric nature of the ICs, the possibility that whole sections of the FDC membrane are extracted, and the role of receptor crowding and receptor height [40]. Even in light of these more complex considerations, we expect our qualitative arguments to still be relevant as the crucial ingredient is that FcγR uses IgG as modulatory link to the IC. We hope our investigation inspires further studies into the biophysical mechanisms regulating affinity and diversity in the GC reaction.

Acknowledgments. The authors would like to thank AGT Pyo, J Merkenschlager, MC Carroll, MC Nussenzweig, and DJ Schaefer-Babajew for valuable discussions. This work was supported in part by Princeton University through the Center for the Physics of Biological Function. This work was also supported by the Weill Cancer Hub East through funding to NSW.

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