What Are the Primary Limitations in B-Cell Affinity Maturation, and How Much Affinity Maturation Can We Drive with Vaccination?

Is Affinity Maturation a Self-Defeating Process for Eliciting Broad Protection?

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Vaccinations are one of the greatest success stories of modern medicine, saving millions of lives since their widespread adoption. However, several diseases continue to elude highly effective vaccination strategies. Chief among these are human immunodeficiency virus (HIV) and influenza (flu), both of which will require vaccines that can guide the creation of highly mutated, broadly neutralizing antibodies (bnAbs). The generation of bnAbs is hindered by our inability to effectively drive the high levels of affinity maturation required to achieve them in a large number of cells. Major limitations placed on affinity maturation derives from the inherent mutability of immunoglobulin genes, the evolved activation-induced cytidine deaminase (AID) targeting mechanisms that exist within them, and biases in targeting of particular epitope B cells.

GREAT DEBATES

What are the most interesting topics likely to come up over dinner or drinks with your colleagues? Or, more importantly, what are the topics that *don't* come up because they are a little too controversial? In ***Immune Memory and Vaccines: Great Debates***, Editors Rafi Ahmed and Shane Crotty have put together a collection of articles on such questions, written by thought leaders in these fields, with the freedom to talk about the issues as they see fit. This short, innovative format aims to bring a fresh perspective by encouraging authors to be opinionated, focus on what is most interesting and current, and avoid restating introductory material covered in many other reviews.

The Editors posed 13 interesting questions critical for our understanding of vaccines and immune memory to a broad group of experts in the field. In each case, several different perspectives are provided. Note that while each author knew that there were additional scientists addressing the same question, they did not know who these authors were, which ensured the independence of the opinions and perspectives expressed in each article. Our hope is that readers enjoy these articles and that they trigger many more conversations on these important topics.

Editors: Shane Crotty and Rafi Ahmed

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The discovery in recent years of antibodies to highly conserved epitopes shared between many or most strains of influenza (flu) (Krammer and Palese 2015) and human immunodeficiency virus (HIV) (Mouquet 2014) have driven interest in the generation of broadly protective vaccines. It has become apparent that a key component to such vaccines is to selectively drive B-cell affinity maturation against broadly protective epitopes (Victoria and Wilson 2015). Affinity maturation is driven by the process of somatic hypermutation (Eisen 2014) most frequently during the germinal center reaction. Simultaneously, there is competition for antigen, and limiting follicular helper T (T_{FH}) cells help the mutationally variant expanded B-cell clones (Victoria et al. 2010). This process is limited by various factors, including both B-cell and variable gene-intrinsic factors and by the context of immune responses. For example, profound shifts in the antibody response can be driven by the context of vaccination, such as biased targeting of conserved epitopes on first exposure to novel influenza strains (Wrammert et al. 2011). Conversely, antibodies arise predominantly to strain-specific epitopes on subsequent exposures (Andrews et al. 2015). Immune history and viral evolution underpin a large proportion of such biased antibody responses. Herein we discuss the intrinsic biological limitations as these factors are coupled to pathogen evolution and evasion, limiting the capacity of affinity maturation to mount broadly protective antibody responses.

DIMINISHING RETURNS

Somatic hypermutation occurs through the deamination of cytosines by the enzyme activation-induced cytidine deaminase (AID). It is well established that AID does not target all cytosines equally; rather it has the ability to discern the context within which a cytosine is located, which alters the likelihood of deamination and thus potential mutations at that site (Yeap et al. 2015). The classical contexts are AID cold spots defined as SYC and the trinucleotides TTC, CAC, GGC, and GAC, in which AID activity is reduced, AID hot spots defined as

WRCY, in which AID activity is increased, and cytosines in all other contexts, which can be considered to be AID neutral (Zheng et al. 2005; Neuberger 2008). Using this as our guide, we can consider that any immunoglobulin gene has an inherent germline mutability determined by the number and location of its cytosines, which will have an impact on all B cells in which it is used and those B-cells' future clones. A simple model for scoring mutability can be determined by a ratio of cytosines existing in hot spots, cytosines existing in cold spots, and cytosines existing in neutral positions divided by the total number of base pairs present in the immunoglobulin gene being considered. It follows that immunoglobulin genes having a higher number of cytosines in hot spots compared with other contexts will have a higher mutability score, meaning a higher likelihood to undergo nonsilent mutations. The idea of immunoglobulin genes having an inherent mutability that differs from gene to gene is not novel (Bonsignori et al. 2016), but one aspect that is rarely considered is that the mutability of a given gene must change as the gene proceeds through the process of somatic hypermutation (Fig. 1). If cytosines in hot spots are the most frequently targeted, and are more likely to produce nonsilent mutations, then the number of cytosines in hot spots will trend downward during a germinal center reaction. This will shift the ratios of cytosines in the varying contexts and decrease overall mutability of the B-cell receptor (BCR). This means the sequence-based targeting of AID likely plays an additional role not previously considered, one in which the immunoglobulin gene sequence protects itself. An already affinity-matured antibody will be protected from losing affinity or specificity by being unable to mutate as much in future germinal center reactions during a recall response. Historically this would serve to preserve B cells that had graduated from a germinal center and thus proven themselves to be protective. This intrinsic protective mechanism leads to situations in which B cells with BCRs that are targeting non-protective or irrelevant epitopes become "fixed" because they are encoded by genes with decreased mutabilities. This limited mutability,

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Figure 1. (A) B cells with B-cell receptors (BCRs) formed from a variety of germline immunoglobulin (Ig) genes are initially selected into a smaller pool of activated B cells against some antigen. These BCRs have differing mutabilities and characteristics with only some capable of eventually forming a broadly neutralizing antibody (bnAb); these are marked by a star. (B) Some of the B cells selected into the smaller pool will have BCRs that recognize immunodominant epitopes, whereas a few others may be capable of producing a bnAb. All of these B cells will go through a germinal center (GC) reaction and the accumulation of mutations, largely in hot spots, during affinity maturation will lower the overall mutability of all genes passing through a GC reaction. The new, less mutable genes are now in memory B cells that will respond on a secondary challenge. (C) Cells targeted to immunodominant epitopes will, through the processes of original antigenic sin and antigenic seniority, dominate the GC responses after a secondary challenge, leading to a cycle of greater expansion and increased victories in GCs. Naïve B cells will also be activated and have a chance to compete with the memory B cells. These two factors make the clones of the already less mutable bnAb precursor less likely to survive GC responses. This greatly reduces the chances of generating bnAbs. SHM, Somatic hypermutation.

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established in the germline and unique for each V gene, decreasing over time, serves as a major limitation on affinity maturation, particularly on chronic or repeated exposure to diverging pathogens such as HIV or flu (Hershberg and Shlomchik 2006).

“FOUNDER” EFFECT

Before returning to the subject of limitations placed on affinity maturation by the diminishing returns associated with inherent mutability, another principal limiting factor must be discussed. This factor can be called, borrowing from evolutionary terms, a “founder’s effect.” Broadly neutralizing antibodies (bnAbs) toward HIV, and somewhat less so those to influenza, have been established and tend to all share some common characteristics that enable their broad breadth of binding (Sadanand et al. 2016). Many HIV bnAbs that have been identified share a feature of having very long, highly charged heavy chain CDR3s, about half are polyreactive, and the majority carry particularly high mutational loads (Gorman et al. 2016; Sadanand et al. 2016). The CDR3s are generally between 16 and 34 amino acids long (Yu and Guan 2014) and the immunoglobulin genes producing these have 20% or more of their predicted germline base pairs mutated. Immunogens that target bnAb germline precursors, particularly for antibodies that bind the CD4 binding site or other locations known to interact with the env protein of HIV, have been used to investigate the characteristics of the naïve, non-affinity matured BCRs (Bonsignori et al. 2016; Jardine et al. 2016). This has made it increasingly apparent that many of the characteristics that are key to bnAbs are present, or have groundwork already present, in their germline precursors (Haynes et al. 2016). Notably, many of these germline BCRs already feature longer CDR3s with charged residues, or residues requiring minimal mutation to become a charged residue. These same characteristics are strictly censored during B-cell development for the purpose of immune tolerance so that naïve B cells with long CDR3s and charged residues causing polyreactivity are rare (Wardemann et al. 2003). Addi-

tionally, these antibodies are almost universally derived from immunoglobulin genes that have high inherent mutabilities, supporting their extensive somatic hypermutation (Fig. 1A). A specific example is CD4bs bnAbs, which are from ontogenies deriving from BCRs containing V_H1-2 or V_H1-46, both which meet the criteria of being highly mutable (Bonsignori et al. 2016). If the polyreactivity frequently observed in these antibodies is because of their extensive levels of somatic hypermutation, which is likely, then all of their features can be accounted for, to a large extent, at the germline level (Briney et al. 2012). Affinity maturation acts to turn a starting material, the germline BCR, into something that still maintains the character of its initial form rather than transforming it into something entirely new. This means the founder effect is itself a major limitation on affinity maturation while also amplifying the impact of inherent mutability as a limitation.

ORIGINAL ANTIGENIC SIN

With this antibody “founder’s effect” acting as a limitation on affinity maturation before the germinal center reaction, there are several other factors that serve to limit it during the process itself. The most prominent two are original antigenic sin and antigenic seniority. These two terms convey similar yet distinct ideas; however, both of them are tied into the mutability of immunoglobulin genes themselves. Original antigenic sin describes the phenomenon wherein the first version of influenza someone is infected with, generally in childhood, will imprint itself on his or her immune memory (Francis 1960). The body will then rely heavily on this large pool of memory when infected with the same or similar viruses in the future. Thus, the immune system ends up hindering a response as large as the initial response from ever occurring again. By forcing an increased reliance on memory B cells, especially with increasing age, original antigenic sin amplifies the impact of decreased mutability with each passing germinal center reaction. Indeed this reduced mutability is perhaps a primary source of original antigenic sin. It is conceivable that the initial germinal

center reaction has the largest impact on the mutability of immunoglobulin genes, because they will serve as a fresh canvas. The immune system's reliance on memory cells, which have reduced mutability, presents a major challenge for effective vaccination strategies with regard to a universal flu vaccine. A vaccine needing to elicit the high level of somatic hypermutation required to create a bnAb will be severely hindered by any previous mutational load on memory cells and may not have the number of naïve cells required to generate an effective bnAb.

ANTIGENIC SENIORITY

In recent years, a new process known as antigenic seniority has been proposed (Lessler et al. 2012). Using mathematical modeling, several groups have tried to more accurately account for why the strain of influenza first encountered in childhood tends to dominate future immune response; antigenic seniority differs from original antigenic sin in that its core tenet is that dominant antibodies rely on repeat exposures to the virus that raised them initially (Lessler et al. 2012; Zarnitsyna et al. 2016). Longitudinal studies, relying on cohorts of different ages, confirmed that the dominant influenza strain circulating when a cohort was young accounted for that cohort's most highly represented antibodies (Miller et al. 2013). Antibody titers to influenza strains appearing when the subjects were older positively correlated with how long the strain had been widespread. Conversely, if a strain had gone extinct, or faded from widespread infectivity, antibody titers against that strain began to decrease over time. The notion that it is the repeated encounters with the same strain, and not just the initial exposure, that skews immune responses further enhances the idea that a loss in mutability over time of activated B-cell immunoglobulin genes presents a major hurdle to effective vaccination strategies.

THE COMMON THREAD; THE MUTABILITY OF IMMUNOGLOBULIN GENES

As previously discussed, every germline BCR can be thought to have some inherent mutabil-

ity that will tend to decrease as the B cell goes through the process of affinity maturation (Fig. 1C). This decrease can be attributed both to the loss of cytosines inside of hot spots as well as the shifting landscape of the sequence. To understand the idea of a “shifting landscape” using ideas from category and systems theory, we propose it is possible that immunoglobulin genes have emergent properties created by the spacing and number of hot spots present. A cluster of hot spots, as can be commonly found within the complementarity-determining regions (CDRs), may raise the likelihood of deamination for a cytosine in any of the hot spots as compared with a cytosine existing within a hot spot surrounded by neutral codons or cold spots. Any time a mutation occurs within one of the hot spots, then the chances of a deamination and following mutation is further reduced within all of the other nearby hot spots. This mutability, derived from a combination of which contexts all cytosines are in and the overall targeting landscape of the gene, is the central limitation on affinity maturation and the greatest challenge to vaccination. Taking into account all previously discussed hurdles, it becomes apparent that they can all act in concert. Initially, a germline precursor having all the right conditions to form into a bnAb must be activated and enter into a germinal center reaction before the process of affinity maturation can begin (Haynes et al. 2016; Jardine et al. 2016); however, bnAbs have, to this point, only been solicited in monoclonal transgenic animal models (McGuire et al. 2016). These approaches normally require multiple vaccinations over time to drive the high amount of somatic hypermutation required. This process will be increasingly hindered with each successive vaccination as the memory cells lose their mutability, contributing to the processes known as antigenic seniority and original antigenic sin. Furthermore, the primary vaccination would have to initially overcome the barrier of selecting B cells with germline BCRs that meet all of the specifications; in a natural polyclonal immune system, this number will be low. These activated cells must then enter into a germinal center and go through affinity maturation, exchanging their

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mutability for mutations that, stochastically, may or may not contribute to bnAb formation, further shrinking the pool of cells that could generate the required antibody. All subsequent vaccination boosting will have to contend with this reduced number of potential candidates that will all also have reduced mutability and, so, reduced chances to acquire the needed mutations. With every step, the chances of everything occurring that is required for bnAb formation becomes increasingly reduced. Another facet is that as targeting to CDR regions is lost then more mutations will accumulate in framework regions. Initially, these framework mutations were thought to be important to an antibody's broadly neutralizing activities (Klein et al. 2013), but research is increasingly showing them to largely be superfluous (Georgiev et al. 2014). More troubling is that these framework mutations are predicted to cause loss of function and thus the B-cell clones, and are likely contributing factors to the high poly- and autoreactivity seen in many bnAbs. Therefore, not only will the loss of targeting and mutability over time in a sequential vaccination decrease the likelihood of a BCR acquiring the breadth of binding it will require to the pathogen, it is also increasing the likelihood it will acquire binding to self, leading it to be negatively selected. The mutability of immunoglobulin genes and its impact on the process of affinity maturation serves as the primary limitation to successful vaccination strategies.

CONCLUDING REMARKS

The sequence-derived inherent mutability of immunoglobulin genes, likely having evolved to protect effective antibodies from mutating away their beneficial changes and from structural destabilization, is a major limitation placed on affinity maturation. Vaccination will have to select a small number of cells that have a mutability high enough to produce a bnAb and then continue selecting those same cells and driving mutation as they lose their ability to mutate, without introducing harmful mutations that either weaken the integrity of the antibody or cause it to become autoreactive. These

strategies will also have to contend with the memory B cells raised by natural infections, or, in the case of flu, previous vaccinations, which will further reduce the chance of selecting a germline cell with high mutability. Considering these factors, it is clear any effective HIV or universal flu vaccination strategy still has many obstacles to overcome. The continued use of animal models and human studies will offer additional illumination of the problem but, currently, it is conceivable to question whether we have the knowledge and technology to create a vaccine that can conquer the limitations placed on affinity maturation by centuries of natural selection.

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