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Review Article

Linkage of Natural Antibody Immunologic Homeostasis to Anticipatory Protection against a Common Pathogen Requires Natural Selection of Immunoglobulin Diversity Gene Segment Sequence

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Abstract

We have recently tested the relative roles of germline versus somatic selection of CDR-H3 sequence in the generation and function of the natural antibody (NAb) repertoires. Our findings indicate that while production of self-reactive NAbs can be independent of germline D_H sequence, their capacity to provide protection against pathogens is not. These findings have potential implications for the rational design of vaccines.

ABBREVIATIONS

AB1.2 – T15-clone-specific antibody; BCR – B cell receptor; CDR-H3 – Complementarity Determining Region 3 of the immunoglobulin heavy chain; ΔD-DFL – Depleted DH locus with a single DFL16.1 gene segment; ΔD-DμFS – depleted DH locus with a single frameshifted DFL16.1 gene segment; ΔD-iD – depleted DH locus with a single mutated DFL16.1 gene segment containing inverted DSP2.2 sequence FR – Framework regions; NAb – natural antibody; OxLDL – Oxidized Low Density Lipoprotein; PC – Phosphorylcholine; RF – DH reading frame; SPF – Specific Pathogen Free; T15-Id+ – T15 idiotype

INTRODUCTION

The term *natural selection* was used by Darwin to describe nature's analogy to *artificial selection*, a process by which animals and plants with traits considered desirable by human breeders are systematically favored for reproduction. Thus, natural selection is considered to be the primary explanation for adaptive evolution. The binding of a cell surface receptor to its ligand typically transduces a signal that affects the function or fate of the cell; *e. g.* , activation, mitosis, differentiation, or death. To maintain the specificity of these downstream effects, each receptor is forced by natural selection to coevolve with its ligand.

At first glance, immunoglobulin (Ig), the B cell receptor for antigen (BCR), appears to be an exception to the rule of natural selection because its ligand (antigen) binding site is designed to vary in sequence and structure. This antigen binding site is created by the juxtaposition of six hypervariable peptide loops, three from the light (L) chain and three from the heavy (H) chain, that are termed complementarity determining regions or CDRs [1-3]. The three CDRs of each chain rest on top of a b-barrel structure composed of two external framework regions (FRs 1 and 3) and two internal FRs (2 and 4). The internal FRs permit stable association of the H and L V domains a help place the surface of the CDRs in the same plane.

A close inspection of the initial IgM repertoire reveals an asymmetric distribution of diversity, with CDR-H3 carrying the majority of the load. The majority of the antigen binding site in the

initial IgM repertoire is actually germline encoded because CDRs 1 and 2 of the H and L chains are entirely contained within the V gene segments and are thus unaffected by VDJ recombination. CDR-L3 is created by V → J joining, but due to constraints in length and a paucity of N addition, this CDR is also largely germline encoded. CDR-H3 is the exception. First in inverse order of importance, the rearrangement of the variable (V), diversity (D) and joining (J) gene segments permits VDJ rearrangement to create a ten to twenty-fold increase in combinatorial V domain diversity in the heavy chain. Second, the extent of imprecision in the VDJ joining process coupled with a wide range of acceptable lengths further enhances the potential for diversity by varying the extent of contribution of germline sequence. Third, and most critically, CDR-H3 diversity is then exponentially enhanced by the terminal deoxynucleotidyl transferase (TdT) catalyzed insertion of non-germline-encoded N nucleotides [4] between the D and the J, and between the V and the D. Initial somatic diversification is thus primarily the province of CDR-H3 which, by virtue of N addition, is the only component of the initial antigen binding site repertoire that has the potential to be truly random.

The power of the V (D) J rearrangement mechanisms used to create diversity has led to a commonly held view that the naïve Ig repertoire consists of a collection of randomly generated antigen binding sites [5]. Rather than natural selection, the operative force for adaptive repertoire optimization was thus postulated to be the product of somatic, or clonal, selection [6,7]. The consequences of antigen reactivity, either positive, neutral, or negative, are thus understood to be a function of chance, with control of antibody production presumed to be primarily modulated by the physiologic state and the developmental stage at which an individual B cell clone carrying the receptor encounters its antigen. This leads to the prediction that the adaptive humoral immune response is primarily dependent on the chance of the antigen finding a randomly generated Ig that binds to that antigen. Thus, the antibody response to antigen by individuals within a species would be expected to vary.

Within the antibody repertoire there exists a subset of immunoglobulins with absent or reduced N addition at the V-D and D-J junctions, thus emphasizing the contribution of germline-encoded sequence to CDR-H3 [8-11]. Many of these N-less immunoglobulins belong to a set of immunoglobulins termed natural antibodies or NAbs. These NAbs are found in the sera of normal individuals in the absence of exogenous antigenic stimulation. The repertoire and reactivity pattern of these NAbs are conserved both within and between species [12] and are remarkably stable [13]. IgM is the dominant NAb isotype, and most, if not all, NAbs appear to be the products of B-1 B cells [14-17].

In mice, NAbs appear to play two very important roles. First, NAbs have been suggested to play a role in normal cellular homeostasis, helping rid the body of cellular and molecular debris [18-20]. And second, NAbs provide one of the first lines of defense against invading pathogens [21-25]. The observation that NAbs are present at equivalent levels in specific-pathogen free (SPF), germfree, and even exogenous antigen-free animals led to the hypothesis that endogenous ligands; i.e. , self antigens, play a major role in the selection of the NAb repertoire [26,27]. That is, due to self-stimulation, the antibody is present in significant amount before the organism has encountered the exogenous pathogen. In some cases, NAbs active in homeostasis also play a role in anticipatory protection against pathogens [28,29].

This linkage between cellular homeostasis and anticipatory pathogen protection led to the hypothesis that the NAb repertoire is a component of the innate immune system [30]. That is, that at least a subset of the NAb repertoire, especially that component that lacks N addition, would be the product of natural selection of the immunoglobulin repertoire. Although the key roles played by the NAbs in host homeostasis and defense are increasingly appreciated, a major remaining question is the nature of the forces that shape the composition of the NAb repertoire. One thesis, which we may refer to as the natural selection hypothesis, holds that the germline composition of the NAb repertoire is critical for its dual function as a protector against both endogenous and exogenous antigens, and thus has been naturally selected during evolution. The antithesis, which we may refer to as the self-antigen-driven or somatic selection hypothesis, proposes that exposure to self-antigen drives the production of dual function NAbs irrespective of germline sequence. In other words, the open question has been whether the driving force for natural selection of immunoglobulin sequence is reactivity to the self-antigen or species memory embedded in the germline of the benefits of predisposing the circulating repertoire of immunoglobulins to contain antibodies with reactivity to antigenic epitopes on one or more ubiquitous pathogens.

One classic example in mice of the dual role of NAbs involves the NAb response to endogenous oxidation-specific epitopes on oxidized low density lipoprotein (OxLDL) /apoptotic cells (AC) and protection against *Streptococcus pneumoniae* [28,19] [31-33]. NAb induced by endogenous OxLDL are capable of preventing potentially atherogenic uptake of this lipid by macrophages, on the other hand it seems to enhance AC clearance in a complement-dependent manner [31,20]; and in humans low levels of IgM antibodies to PC have been associated with a higher risk of cardiovascular disease [29]. NAbs bearing the germline encoded T15 idiotype (T15-Id) appear to be selected into the peripheral B cell repertoire and expanded in response to OxLDL [30,33]. T15-Id$^+$ NAbs also bind to phosphorylcholine (PC) present on the cell wall of *Streptococcus pneumoniae* [22,34]. T15-Id antibodies constitute 60-80% of the natural anti-PC response [35-38]. The T15-Id is conserved across multiple mouse strains and is tightly associated with the use of a specific V_H (*V_HS107.1*) and a specific V_L (*Vk22*) [39]. Thus*V_HS107.1* and *Vk22* encode four of the T15 CDRs in their entirety (CDR-H1&2 and CDRL1&2) and most of the fifth, CDR-L3 (Figure 1). Disruption of the *V_HS107.1* gene, with loss of two of the T15 CDR-H sequences, results in an inability to mount a protective immune response to *S. pneumoniae* [40]. Although many antibodies can bind PC, those containing the germline canonical T15-Id confer optimal protection against lethal *S. pneumoniae* bacteremia [41] and fatal sepsis [42].

In common with many other B-1a immunoglobulins, canonical anti-PC T15 CDR-H3s lack N-region addition and use their D_H, in this case *DFL16.1*, in only one of six potential reading frames, RF1 (Figure 1 and [8]). These findings raised the possibility that the complete germline sequence of DFL16.1 in general, and

of RF1 in particular, is critical for creating a category of NAbs with naturally selected germline CDR-H3 sequence, as dictated by the use of DFL16.1, that would both provide for protection against atherosclerosis by preventing the uptake of OxLDL and, at the same time, provide protection against a common epitope on the surface of *S. pneumoniae*, and thus provide anticipatory protection against this ubiquitous pathogen.

To test the hypothesis of natural selection-dictated dual protection, we used a panel of BALB/c mice with altered D_H alleles [43-46] to both qualitatively and quantitatively test the relative roles of germline versus somatic selection of CDR-H3 sequence in the generation and function of the anti-OxLDL, anti-PC and T15-Id^+ NAb repertoires.

We had previously used techniques of cre-loxP based gene targeting on a BALB/c ES cell line to delete 12 of the thirteen D_H gene segments in the D_H locus, thus retaining only the*DFL16.1* segment (*ΔD-DFL* mice), which in its physiologic state preferentially uses the tyrosine-enriched reading frame, RF1, that contributes to the canonical T15-Id+ anti-PC, anti-OxLDL repertoire. This mouse would be expected to have a high likelihood of generating antibodies with a classical T15 CDR-H3-type sequence.

A second D-altered mouse contained only a single *DFL16.1*gene segment (*ΔD-DμFS*) that had been modified by means of two frameshift single nucleotide insertions to enhance use of an alternative reading frame, RF2, enriched for valine, in place of tyrosine. One of the frame shift insertions introduced a termination codon at the 3' end of the *DμFS* gene segment. Thus, although the core of the DFL16.1 RF1 sequence remained intact, creation of a CDR-H3 with a canonical T15 sequence would require both extensive nucleotide nibbling at the 3' end of the D_H segment and extensive N nucleotide addition at the DàJ junction. Thus, in this mouse, production of the classical T15 CDR-H3 amino acid sequence would require TdT-catalyzed N addition to mend DFL16.1, a feature of B cells of postnatal origin.

The third D-altered mouse (*ΔD-iD*) encoded an inverted *DSP2.2* gene segment and completely lacked core DFL16.1 RF1 sequence. Creation of a classical T15 CDR-H3 amino acid sequence would require complete rebuilding of DFL16.1 amino acid sequence by means of N addition. Thus, creation of T15 activity in this mouse would rest solely on clonal, somatic selection since the contribution to CDR-H3 of naturally selected DFL16.1 sequence had been eliminated by gene targeting.

Using strains from our panel of D_H-altered mice to test the requirement for the *DFL16.1* RF1 sequence in the generation of NAbs specific for OxLDL, we quantified the serum titers of IgM anti-OxLDL by D_H genotype. In unmanipulated mice, we found that the physiological levels of anti-OxLDL antibodies were indistinguishable among the different strains, irrespective of the availability of evolutionarily conserved *DFL16.1* gene segment sequence (Figure 2). The anti-atherogenic potential of anti-OxLDL NAbs generated under varying levels of *DFL16.1* availability proved equally efficacious to WT in blocking binding of OxLDL to macrophages [1]. These results suggested that both anti-OxLDL NAb serum levels and functionality had apparently been qualitatively and quantitatively unaffected by enhancement, alteration or the complete elimination of germline *DFL16.1* gene segment sequence usage. Thus, the efficacy of cellular homeostasis by this classic B-1 NAb response appeared independent of naturally selected germline CDR-H3 sequence, pointing to somatic, clonal selection driven by a self-antigen as the operative force.

On the other hand, there was a direct relationship between anti-PC titer and the likelihood of using DFL16.1 in its germline form (Figure 2). This suggested that the availability of B cells incorporating germline encoded *DFL16.1* RF1 sequence into

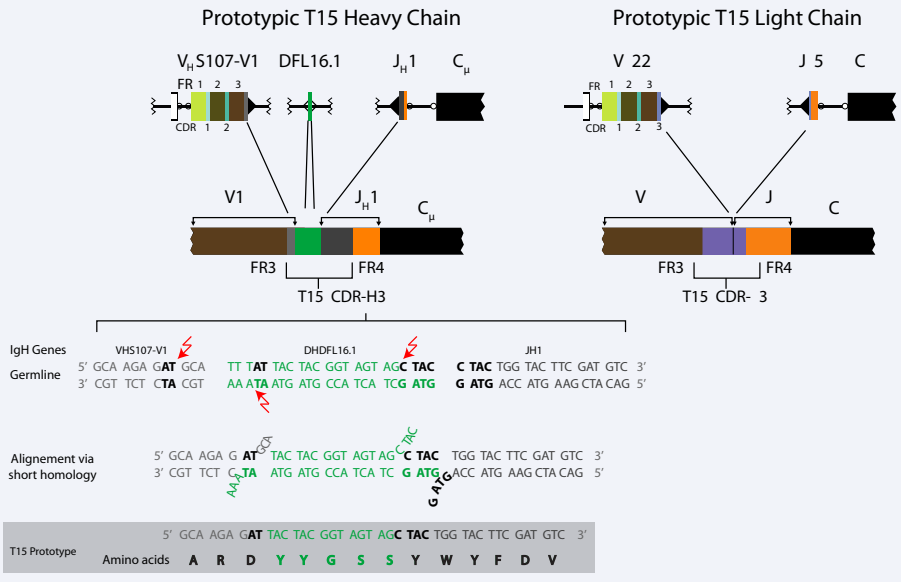

Figure 1 Creation of the prototypic T15 antigen binding site. (Left Panel) A prototypic T15 heavy chain variable domain is created by the joining of the D_HDFL16.1 in reading frame 1 to V_HS107.1 and J_H1 joining. There are no N nucleotides. The amino acid sequence of the CDR-H3 region of the prototypic T15 H chain V domain is shown (in gray). Depicted is a closer look at the sites of short homology between the V_HS107.1-D_HDFL16.1 and D_HDFL16.1-J_H1 junctions (bold) that drive the rearrangement of D_HDFL16.1 into reading frame 1. (Right Panel) A prototypic T15 light chain variable domain is created by $V_κ$22-$J_κ$5 joining.

their Ig H chains might be directly influencing the physiological production of natural anti-PC antibodies. We also found a correlation between the availability of *DFL16.1* reading frame 1 and the levels of T15-Id+ NAbs (Figure 2). While there was a relatively stable number of a B-1a cell bearing anti-PC BCR in the peritoneal cavity, the frequency of T15-Id+ B-1a cells directly correlated with the likelihood of access to DFL16.1 reading frame 1 sequence. These data indicated that the potential to secrete T15-Id+ antibodies, but not total anti-PC, is both qualitatively and quantitatively dependent on the availability of naturally selected DFL16.1.

An elegant confirmation of this finding was obtained by sorting, sequencing and analyzing the CDR-H3 of anti-PC T15-Id+ B-1a cells from the peritoneal cavity of homozygous D_H-altered mice and WT. The classical T15 CDR-H3 amino acid sequence was obtained only from B-1a cells that stained brightly for PC-DEX and AB1.2 (T15-Id+) (Figure 3). Further, the T15 heavy chain prototype was found only in B-1a cells derived from mice that carry the *DFL16.1* gene segment sequence in proportions dependent on its availability for usage (Figure 3B). Strikingly, the prevalence of N-addition increased, and V_H/J_H usage became more diversified, as the complete sequence of *DFL16.1* in RF1 became less available to the D_H-altered mice. Among the sequences isolated from AB1.2/PC-DEX+ B-1a cells from the DD-DmFS mouse, which has a damaged DFL16.1 sequence, we found an example of a clone that had recreated the classic T15 anti-PC amino acid sequence by means of N addition [1]. No such clones were found in the sequences obtained from the DD-iD mouse, which completely lacks DFL16.1 (Figure 3B). Together these findings suggest that while somatic, clonal selection pressure is being exerted to create the classic T15 anti-PC CDR-H3 sequence, the power of N addition is sufficient only to help correct a damaged sequence, not one that is absent. Unlike anti-OxLDL antibodies, production of T15 anti-PC CDR-H3 thus appeared dependent on natural selection of germline immunoglobulin sequence.

Changing the germline sequence of the D_H locus thus permitted production of both anti-OxLDL antibodies and anti-PC antibodies, but the damage or absence of DFL16.1 reading frame 1 sequence inhibited or did not allow production of T15-Id+ antibodies with dual anti-OxLDL, anti-PC reactivity. Although, we had observed maintenance of potentially protective NAbs against atherogenesis in the response to the self-antigen, the production of protective anti-PC antibodies was impaired by the absence of access to DFL16.1 core sequence. Even exposure to live bacteria in a life-threatening situation proved insufficient to elicit classic T15-Id anti-PC antibodies in the absence of naturally selected immunoglobulin sequence [1].

These studies provide an answer to the question of whether natural selection of the immunoglobulin repertoire plays a role in resistance to disease. In the absence of evolutionary conserved D_H sequence, we find that somatic selection continues to elicit a set of NAbs capable of providing protection against a self-antigen by product of cellular homeostasis. Thus this function of the B-1a B cell subset appears independent of natural selection. Instead it appears driven by altered self-antigen stimulation.

In contrast, in the absence of naturally selected germline sequence, the B-1a population proved incapable of providing that first line of defense against infection that is normally contributed by the natural antibody repertoire. PC epitopes are found on endogenous as well as exogenous antigens. Accordingly, it has been suggested that the T15 clonotype has been conserved during evolution because of its value both for protection against host damage by oxidatively modified self-structures and for defense against infection with PC-bearing pathogens [47]. However, the severing of the relationship between the production of NAbs against OxLDL and NAbs against PC in our D_H-altered mice indicates that the concordance between these activities requires access to conserved germline D_H sequence content.

In conclusion, D_H gene segment sequence can both qualitatively

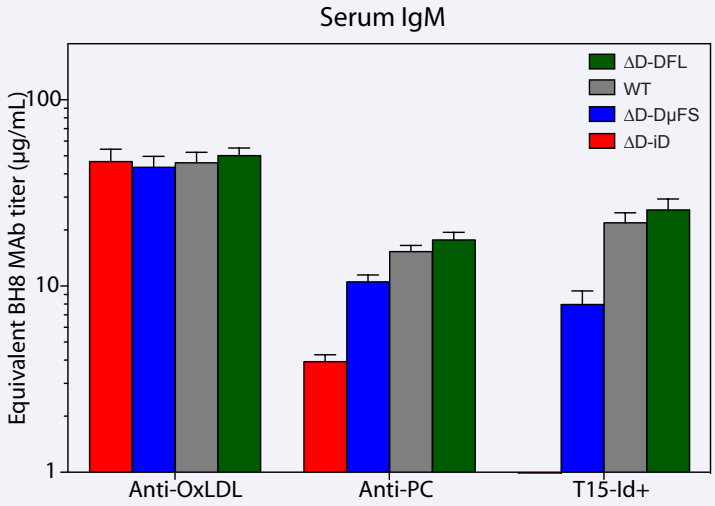

Figure 2 Loss of evolutionary conserved DH sequence quantitatively decreases the serum levels of anti-PC and T15-Id NAbs, but not anti-OxLDL NAbs. The median serum concentration of natural IgM anti-OxLDL (Left), anti-PC (Center) and T15-Id+ (Right) by mouse genotype are plotted as a function of the relative availability of DFL16.1 in RF1 compared to WT, which ranges as follows: ΔD-iD << ΔD-DμFS < WT<< ΔD-DFL. The levels of IgM antibodies for each mouse strain are shown as an equivalent titer (μg/ml) to the BALB/c IgM anti-PC producing hybridoma BH8.

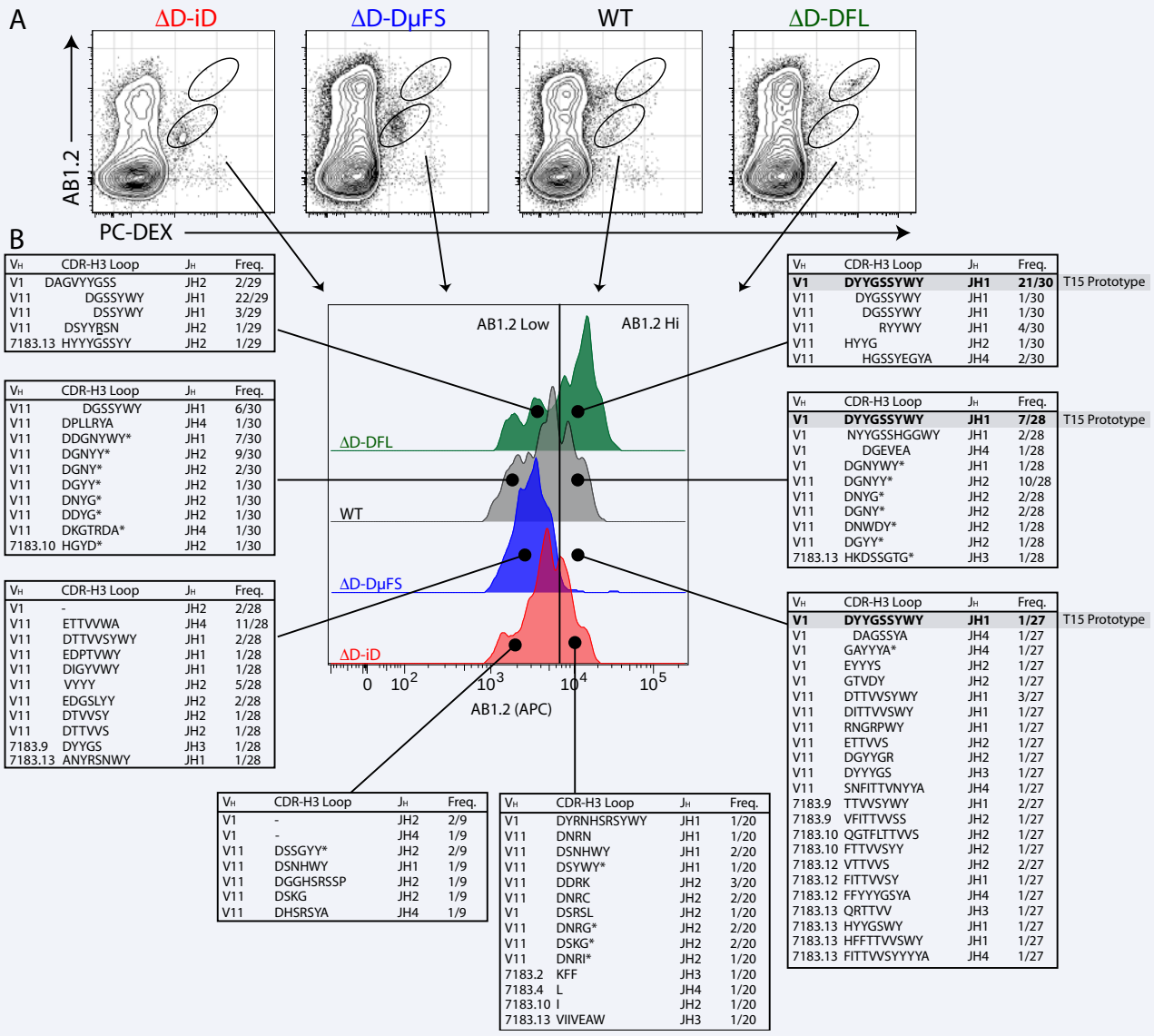

Figure 3 **The frequency of classical T15 CDR-H3 amino acid sequence in PC-DEXHI B-1a cells is directly proportional to the availability of DFL16.1 RF1 gene segment. (A)** Representative flow cytometry dot plots of PC-DEX+AB1.2+ (T15-Id+) PerC B-1a cell population sorted for CDR-H3 sequencing. **(B)** CDR-H3 amino acid sequences of PC-DEX^{low}/AB1.2^{low} and PC-DEX^{hi}/AB1.2^{hi} B-1a cells from each of the mouse strains. The T15 prototypes are shown in gray. The stars (*) indicate VDJ sequences in which the DFL16.1 gene was not present in the case of the WT mice, or VDJ sequences that no DH gene was identified in the case of the DH-altered mouse strains.

and quantitatively regulate the antigen binding site features of NAbs and thus control the consequences of self-antigen driven antibody production. Our results support the view that in order to provide protection against organisms bearing target epitopes that are difficult to alter, such as PC, natural selection has shaped the germline immunoglobulin repertoire to link anticipatory protection to basic antigen-driven cellular homeostasis. These results suggest that the antibody repertoire is not the *tabula rasa* that a view of repertoire diversification as random would imply. Harnessing the power of this naturally selected repertoire to medical interventions such as vaccination and immunotherapy may yield new forms of treatment for common diseases. Conversely, the absence of specific immunoglobulin germline sequence may help explain why some forms of vaccination have been ineffective and why our species is sensitive to some pathogens, but not others.

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