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Review article

Immunogenic properties of immunoglobulin superfamily members within complex biological networks

Josué Odales, Jesus Guzman Valle, Fernando Martínez-Cortés, Karen Manoutcharian *

Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México (UNAM), AP 70228, Ciudad Universitaria, México, DF 04510, Mexico

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ABSTRACT

Antibodies, T cell receptors and major histocompatibility complex molecules are members of the immunoglobulin superfamily and have pivotal roles in the immune system. The fine interrelation between them regulates several immune functions. Here, we describe lesser-known functions ascribed to these molecules in generating and maintaining immune response. Particularly, we outline the contribution of antibody- and T cell receptor-derived complementarity-determining region neoantigens, antigenized antibodies, as well as major histocompatibility complex class I molecules-derived epitopes to the induction of protective/therapeutic immune responses against pathogens and cancer. We discuss findings of our own and other studies describing protective mechanisms, based on immunogenic properties of immunoglobulin superfamily members, and evaluate the perspectives of application of this class of immunogens in molecular vaccines design.

1. Introduction

The immunoglobulin (Ig) superfamily is a large functionally diverse group of proteins which bear a common Ig domain, consisting of two anti-parallel β-sheets stabilized with a disulfide bond [1]. Antibodies (Abs), T cell receptors (TCRs) and major histocompatibility complex (MHC) class I or class II molecules are members of Ig superfamily that play critical roles in immune response network [1,2].

Since the discovery of the therapeutic potential of serum from animals exposed to attenuated pathogens, more than a century ago, huge progress in the development of Ab-based therapeutics has been made. Many Abs are currently being used to treat several major pathological conditions: cancer, autoimmune, cardiovascular, infectious and neurodegenerative diseases, and the mechanisms of action of Ab treatment have been reviewed elsewhere [3–8].

TCR and Ab molecules contain three complementarity-determining regions (CDRs), per variable domain, which are responsible for antigen (Ag) recognition. CDR3 is the most diverse region, in terms of sequence and length, and is considered the most important in determining the specificity of a given Ab or TCR [9]. B lymphocytes often undergo affinity maturation after initial encounter with Ag, subsequently they produce new, slightly modified Abs with increased affinity. This implies that the Ag-Ab interaction is almost perfect, i.e., the six CDRs of a given Ab would be the "specular image" of the interaction established with a specific Ag. For decades, there has been compelling evidence of CDR-specific T and B lymphocyte activation. This concept is partially based on the proposed Ab network, pioneered by Jerne in 1974 (Fig. 1A), which suggests that one antibody (Ab1) will induce an effective immune response that generates a second Ab (Ab2: Ab2α targeting the region close to the Ag-recognizing site of Ab1 and Ab2β directed against CDRs of Ab1), thus initiating the idiotype-anti-idiotype network [10]. In this manner, the Ab2β CDRs carry the internal image of the original Ag, and form the basis for the concept of molecular mimicry [11].

Here, we aim to focus on seldom mentioned immune functions, particularly immunogenic properties, attributed to Ab, MHC and TCR molecules. The immunogenicity of TCR and Abs, evidenced by experimental data, as well as the potential applications in biotechnology and vaccine development are discussed. We also analyze the roles played by anti-idiotypic responses during the activation of naïve B/T cells,

Abbreviations: Ab1, Idiotypic antibody; Ab2, Anti-idiotypic antibody; ADAs, Anti-drug antibodies; BCR, B cell receptor; CDRs, Complementarity-determining regions; CTL, Cytotoxic T lymphocyte; HACA, Human anti-chimeric antibody; HAHA, Human anti-human antibody; HAMA, Human anti-mouse antibody; HCDR3, Immunoglobulin heavy-chain complementarity-determining region 3; LCMV, Lymphocytic choriomeningitis virus; MHC, Major histocompatibility complex; nTreg, Natural regulatory T cells; TCR, T cell receptor; VELs, Variable epitope libraries.

* Corresponding author.
E-mail address: karman@unam.mx (K. Manoutcharian).

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memory maintenance and the contraction of adaptive immune responses. As well, the implicit immunogenicity of MHC molecules in transplantation and cancer fields are addressed.

2. MHC molecules in immunity

MHC molecules are proteins that play an essential role in T lymphocyte activation. TCRs interact, primarily, in a diagonal docking mode, where germline-encoded CDR1 and CDR2 in the TCR β-chain

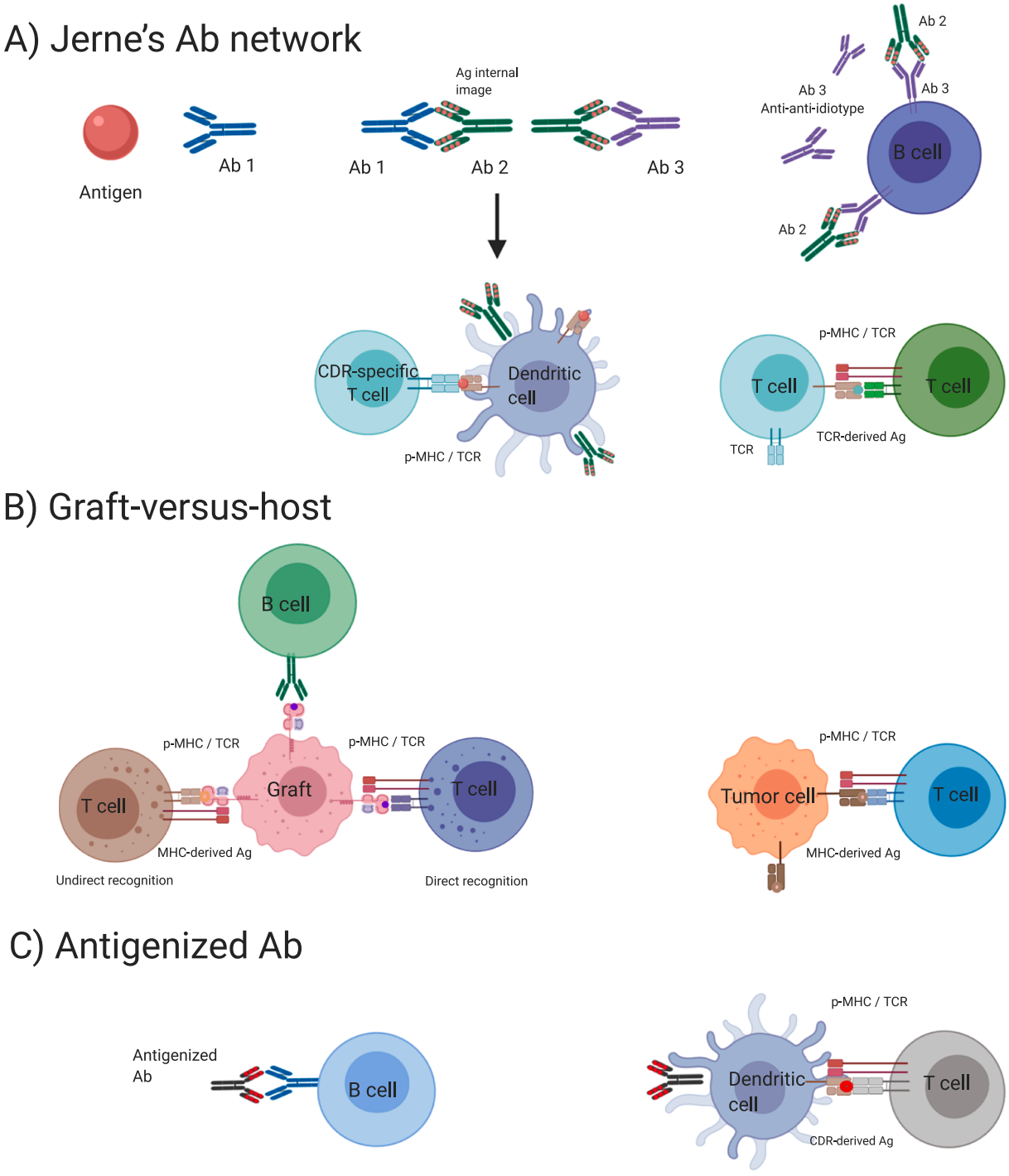

Fig. 1. Basic interactions between Ig superfamily members within immunological network. (A) According to Jerne's network theory, an antibody (Ab2) can bind to the variable region of antigen (Ag)-specific Ab (Ab1) and trigger a successive cascade of anti-anti-antibody production (Ab3). The anti-idiotypic Ab2 carries the internal image/mimotopes of the original Ag in CDRs and is capable to generate anti-anti-idiotypic B and T cell responses reinforcing the immune response to the original Ag. This class of immunogens (Ab2) was used as a vaccine against cancer and several pathogens. Similarly, the TCR beta chain (idiotypic TCR) generates TCR-specific Ab and anti-idiotypic Ag-specific T cell responses. (B) In transplant rejection, within graft-versus-host (GVH) interactions, apparently both auto- and allo-immunity are involved. The B cells produce MHC and non-MHC Abs, as well as Abs against mismatched minor Histocompatibility Antigens (mHC). The T cells can damage the graft by directly recognizing donor's MHC or by eliminating target cells through p-MHC/TCR interaction, where peptides are derived from MHC molecules (undirect recognition). By a similar manner, the T cells may eliminate tumor cells through recognition of self MHC-derived peptides. (C) The antigenized Abs are immunoglobulins where T cell epitopes are inserted within CDRs, which convert them in effective vaccine immunogens targeting pathogens and tumor cells.

interact with α1 domain helixes of either MHC class I or II molecules; and CDR1 and CDR2 from the TCR α-chain recognize, preferentially, the α2 or β1 domains of MHC class I or II molecules, respectively. The hypervariable CDR3 region in both chains of the TCR directly recognizes the presented peptide, with less interaction with MHC regions. The CD8 and CD4 coreceptors focus TCR recognition in the context of MHC molecules by directly binding to the α3 and β2 domains found in MHC class I and II molecules, respectively [12,13].

MHC restriction of the TCR is a critical event in T lymphocyte activation [14]. Two models aiming to explain the mechanistic basis of MHC restriction have been developed: the germline-encoded model and the selection model. The germline-encoded model establishes that MHC and TCR variable gene segments coevolved, and that there is a bias towards MHC recognition of certain "interaction codons" or triad residues in V segments. The selection model proposes that the TCR has no intrinsic reactivity to MHC molecules, but rather MHC reactivity is conferred by signaling constraints imposed by the coreceptor molecules during thymic positive selection [15,16]. These two models are not mutually exclusive, and together provide a general and more complete model of MHC restriction [17]. Similarly, several models have been proposed to describe optimal affinity during pMHC-TCR interaction: kinetic-proofreading and serial triggering models; along with the prediction that there is an upper and lower limit to the half-life during pMHC-TCR complex binding, which narrows the range of optimal affinities leading to T cell activation [2].

During organ transplantation, determining MHC compatibility between the donor-derived organ and recipient is a crucial step to reduce rejection mediated by graft-versus-host interaction. Today, the presence of donor-derived HLA-specific Ab and T cell responses are suggested as part of the leading causes of organ rejection [18]. Preexisting organ-specific Ab responses lead to acute Ab-mediated rejection, even though Ab responses could be elicited any time after organ transplantation; furthermore, direct or indirect T cell-mediated organ rejection provides other mechanisms that act in conjunction with Ab responses leading to the damage of the transplanted organ or finally, to the patient death [19,20], (Fig. 1B). Also, autoimmunity, mediated by non-HLA Ab responses following solid organ transplantation, contributes to transplant rejection [21].

Cancer cells generally present modified versions, or abnormal expression of MHC molecules, as seen through loss of heterozygosity or loss of expression, which are associated with immune editing of tumors, and may contribute to cancer evolution and immune escape [22,23]. In line with the abovementioned immune mechanisms of organ rejection, and with the potential immunogenicity of MHC molecules (Fig. 1B), we were the first, to our knowledge, to generate cancer vaccine immunogens, based on peptides derived from MHC Qa-2 and H2-K molecules, and to show their protective effects targeting the tumor as a transplanted organ in a mouse model of breast cancer [24]. We have demonstrated significant inhibition of the tumor growth and the reduction of metastatic lesions in the lungs of immunized animals [24]. Therefore, harnessing the immunogenic properties of MHC molecules might provide an entirely new direction to treat cancer.

Furthermore, newly synthetized MHC class I α chains contain signal peptides that do not form part of the mature protein. These signal peptides remain in the endoplasmic reticulum after cleavage from the α chain, but afterwards are processed by proteolytic cleavage via signal peptide peptidase, and their amino-terminal portion is released into the cytosol. The MHC class I-derived signal peptide reenters the normal MHC class I antigen processing and presentation pathway and is finally loaded, specifically, on the non-classical HLA-E molecule whose function is immunosurveillance [25]. This mechanism indirectly evaluates MHC class I protein level translation. The NK and $CD8^+$ T cell CD94/NKG-2A inhibitory and CD94/NKG-2C activating receptors oversee the production of peptide-HLA-E complexes [26,27]. In addition, inhibitory KIR family receptors on cytotoxic cells directly recognize MHC class I molecules and function by protecting normal non-stressed cells from cytotoxic lysis [28]. Thus, MHC molecules have several immunological functions beyond the immunological synapse with T lymphocytes.

3. Immunogenicity of antibodies

Muromonab-CD3 (OKT-3) was the first anti-human CD3 monoclonal antibody approved for human use by the Food and Drug Administration (FDA) in 1986 [29]. It was used to prevent organ rejection after transplantation by primarily reducing T cell functions. In 86% of patients treated with the murine Ab, human anti-drug antibodies (ADAs) were induced, a phenomenon known as human anti-mouse antibody (HAMA) response [29]. The ADA response decreases the efficacy of the treatment and induces adverse effects such as hypersensitivity-type reactions [30]. These findings encourage efforts to reduce Ab-related drug immunogenicity in order to develop better and safer drugs. This led to Ab chimerization which is a process where xenogeneic Ig constant regions are replaced by human Ig constant sequences, in this manner Ab-associated immunogenicity is reduced. Rituximab (Rituxan) was the first FDA-approved chimeric Ab in 1997 and is a CD20-specific Ab used to treat several B lymphocyte-related conditions [31]. Unfortunately, an ADA response was also generated against Rituximab. This new immune response, called human anti-chimeric antibody (HACA), was directed to the remaining non-human epitopes present in the variable regions of the chimeric Abs, e.g., murine-derived epitopes in Rituxan [32].

HAMA and HACA anti-drug responses fostered efforts to reduce the immunogenicity of clinically relevant Abs as much as possible. One strategy, known as Ab humanization, consists of grafting CDRs from an Ag-specific non-human Ab to a human Ab. In this manner, humanized Abs maintain Ag-specificity by keeping the CDRs of the original non-human Ag-specific Ab and reduce immunogenicity by containing the human sequences for both the constant and Ig variable framework regions. These findings led to the more common use of humanized Abs compared to murine or chimeric Abs [33]. Furthermore, technological advances have now enabled the generation and use of fully human Ab treatment. Adalimumab (Humira) was the first fully human anti-TNF therapeutic Ab, generated by phage display technology [34]. Surprisingly, human anti-human antibody (HAHA) responses were indeed induced with adalimumab treatment and ADAs were measured in up to 87% of patients, reducing the efficacy of the treatment [35]. We could assume that the immunogenicity associated with humanized or human Abs is based on CDR epitopes which generate ADA responses [36]. CDR-derived epitopes are thus genuine neoantigens, randomly generated, and are not subject to central tolerance mechanisms. Deimmunization of Abs has been further sophisticated by immune analysis with considerations for $CD4^+$ T cell epitopes in Ab variable regions, which has proved to be associated with the generation of high affinity ADAs. Modifications in variable region sequences of Abs, to reduce the immunogenicity of $CD4^+$ T cell-associated epitopes, diminished HAMA responses while maintaining Ag-binding capability [37].

The natural humoral immune response directed towards Ab CDRs in the case of humanized and fully human Abs, indicates that Abs also function as Ags for B and T cells (Fig. 1C). During the 90′s, Zanetti and collaborators proposed that Abs could be antigenized by grafting pathogen- or non-pathogen-derived protein sequences into CDRs [38]. The initial experimental findings demonstrated the antigenic and immunogenic potentials of antigenized Abs, by eliciting efficient helper and cytotoxic T lymphocytes (CTLs), as well as B cell immune responses to the epitopes present in the CDRs of Abs [38–41]. Antigenized Abs demonstrated that Igs are an exemplary protein platform to present foreign peptides to the immune system in a CDR-dependent manner, in particular, when HCDR3 is used, whereby the original conformation of the V domain and the epitope are maintained [39]. Recently, potent T cell responses associated with favorable clinical outcome in a clinical trial have been reported, where melanoma patients received a DNA vaccine bearing human IgG1, carrying T cell epitopes grafted into CDRs [42].

To the best of our knowledge, we were the first to develop antigenized Abs as vaccines using phage display technology: we expressed antigenized Ig VH region, which carried a *Taenia crassiceps* PT1 10-mer epitope inserted in all three HCDR loops, on the M13 bacteriophage surface [43]. Later, we developed a novel vaccine approach based on a new class of vaccine immunogens, called Variable Epitope Libraries (VELs), for the treatment of diseases caused by antigenically variable pathogens and cancer [24,44–46]. VELs are combinatorial mutant epitope libraries, generated by substituting 3–5 defined amino acid residues within the epitope of interest with any of the natural 20 amino acids. We were able to generate recombinant M13 phage immunogens, expressing the VEL-based, HIV-1-derived immunodominant CTL epitope, along with 5 amino acids from Ig frameworks 3 and 4, adjacent to the HCDR3. To generate a DNA vaccine immunogen, we cloned the VEL into the HCDR3 region, in order to express the VEL within the complete Ig-derived H chain. Immunizations with DNA and recombinant phage elicited broad and long-lasting epitope specific $CD8^{+}IFN\gamma^{+}$ T cell and Ab responses, respectively [44,45]. Importantly, sera obtained from mice immunized with VELs were able to neutralize half of a Tier-2 HIV-1 reference panel [45]. We also confirmed the anti-Id nature of these Abs by isolation of an Ab-binding peptide motif that resembles the original HIV-1 epitope after screening of immune sera against phage display random peptide libraries [45]. In cancer-related research, we generated Survivin and MHC class I protein T cell epitope-based VELs, which reduced tumor size and metastatic burden after therapeutic vaccination, in the mouse 4T1 breast tumor model [24,46]. These two VELs expressed the recombinant peptide as fusions to the M13 phage major coat protein and were constructed in the context of FR3-HCDR3-FR4. Our studies in mouse models confirmed Zanetti's idea that sequences introduced into Ig CDRs represent an adequate platform for generation of potent and functional immune responses to peptides grafted into HCDR loops.

For over 30 years, Ab-based therapy has been approved by medical regulatory agencies worldwide and has been used in various clinical settings. Ab-based therapy is widely considered a safe and effective medical treatment; however, adverse effects in patients have been reported [47,48]. To our knowledge, long-term studies on the undesirable effects of Ab treatment have not been conducted, thus we are most likely ignorant to the consequences of manipulating the immune system. Although several mechanisms of action have been described for this treatment modality, in most cases, these can be reduced to (i) an interaction-blocking agent and/or (ii) a targeted drug with Fc-related immune effector functions. However, other unorthodox therapeutic approaches have also been explored such as anti-idiotype vaccines and intravenous immunoglobulin (IVIG) treatment.

The anti-idiotype vaccine concept is based on the idiotype/anti-idiotype cascade proposed by Jerne (Fig. 1A), where Ab2 surrogates the physico-chemical interactions established by the Ag-Ab complex. This is particularly interesting when utilizing non-protein antigens such as lipids, nucleic acids or carbohydrate epitopes, as these are less immunogenic than protein-derived epitopes. Preclinical studies using Ab2 have shown effective B and T cell responses against the original antigen [49,50]. However, clinical studies employing anti-idiotype vaccines have provided inconclusive results in cancer immunotherapy: there is no FDA approved anti-idiotype vaccine in the United States. Racotumomab (Vaxira) is an IgG1 murine Ab2 against *N*-glycolylneuraminic acid glycoconjugates, such as cancer neoantigen NeuGcGM3 ganglioside [51]. In a recent randomized phase II/III trial study, 86 non-small cell lung cancer patients treated with Vaxira demonstrated superior overall survival and tumor growth progression-free survival in comparison to the placebo group, with 8.23 vs. 6.8 and 5.33 vs. 3.9 months, respectively. Also, patients who elicited an effective humoral response to NeuGcGM3 showed longer median survival time [51]. These results led Vaxira to be the first approved anti-idiotype vaccine, with permission granted in Cuba and Argentina. A phase III clinical trial using Vaxira is currently undergoing (www.clinicaltrials.com).

IVIG is a blood product consisting primarily of a mixture of IgGs from thousands of healthy donors. The main indication for IVIG is in replacement therapy, where low doses (300 mg/kg, every 3 weeks) are administered to patients with immunodeficiency-related conditions, with the purpose of providing passive immunity against pathogens [52]. Furthermore, IVIG has immunomodulatory effects at high concentrations (2 g/kg/month), where it has been used for the treatment of autoimmune or inflammatory disorders [53,54]. Interestingly, positive preliminary data on IVIG therapy in pediatric COVID-19 patients have been reported recently, and its use in other groups of patients is under consideration [55]. The mechanism of action for the immunomodulatory effects are not well established but many Fab- and Fc-dependent mechanisms are presumed to be involved, e.g., Ab neutralization, cytokines, complement molecules, blockade of neonatal Fc receptor and Fc activating receptors [56,57]. Also, the presence of T cell epitopes for natural regulatory T cells (nTreg) in the primary IgG sequence is presumed to be involved in increasing the nTreg population, concomitant to reduction of the proliferative T cell response [58]. The induction of these nTregs that recognize highly promiscuous MHC class II *T*-cell epitopes or "Tregitopes" in the Fc fragment of IgG, as a possible mechanism for the immunosuppressive activity of IgG, may have clinical implications; for example, for hemophilia treatment, to avoid immunogenicity and induce immune tolerance, the recombinant factor VIII (rFVIII) and rFIX, fused to the Fc domain of IgG, have been developed as therapeutic agents with longer-lasting circulating half-life [58,59].

Regarding TCRs, their αβ protein chains are limited to expression as a membrane anchored complex, not in a soluble form, and are functionally restricted to MHC molecules. For these reasons, the TCR has not been exploited in the biotechnology field as much as Abs. However, based on the similarity in immune functions and structure with the B cell receptor (BCR)/Ab, we could expect similar immunogenic properties to be mirrored by the TCR. Indeed, it has been proven that a Morbillivirus nucleocapsid protein-specific $CD8^{+}$ T cells, stimulated in vitro, process and present its own TCR-derived peptides, to both anti-idiotypic $CD8^{+}$ and $CD4^{+}$ T cells, confirming that Ig-derived CDR epitopes are immunogenic [60,61].

4. Interrelation of immune functions between members of the Ig superfamily: MHC-BCR/Ab-TCR

Interaction amongst these three members of the Ig superfamily goes beyond their roles in lymphocyte activation or aiding the adaptive arm of the immune system (Fig. 1). One possible implication is contraction of the immune response, the final phase after efforts of the immune system to eliminate a pathogen and achieve homeostasis. After initial encounter with an immunogen, T cells and B cells undergo clonal proliferation, this implies a simultaneous expansion in CDR neoantigens that may elicit an effective anti-idiotypic response. This natural anti-idiotype cellular and humoral immune response might function as a contraction element of the immune system, eliminating effector lymphocyte clones. The specific elimination hypothesis for contraction of the immune response could explain experimental evidence for epitope-specific CTL elimination, after prolonged exposure to a lymphocytic choriomeningitis virus (LCMV)-derived NP396 CTL epitope but not to exposure to other LCMV CTL epitopes [62]. If elimination occurs in differentiated effector or memory cells, it would be subject to further research. Other T cell dysfunctional processes may be involved such as exhaustion of epitope specific CTLs, which has been also demonstrated in the same model [63].

Either clonal deletion, exhaustion or other T cell dysfunction processes may be occurring in cancer, which may reduce the repertoire of effector lymphocytes. Experimental evidence came from studies in 2016 where tumor-infiltrating lymphocytes were only able to recognize 2 of 126 tumor-derived neoantigens from a stage IV melanoma patient [64]. The authors demonstrated that an outsourced naïve pool of T cells from healthy donors, indeed, has idiotypes that respond to those neoantigens,

in contrast to the patient-derived own T cells [64].

Other experimental clues concerning the idiotype-anti-idiotype network came from two separate experiments, which demonstrated specific idiotypic response inhibition after anti-idiotype intervention against two hapten groups, azophenylarsonates and phosphorylcholine, respectively [65,66]. The proposed mechanism involved a hapten-specific idiotype BCR-Ab2 blocking interaction for hapten-specific inhibition of B lymphocyte responses [65,66]. A similar theoretical mechanism might occur in the event of Ab recognition and blockade of either the TCR or the peptide-MHC complex; this could explain the reduction of the functional T cell repertoire, described above. Furthermore, experiments in which T cells interact with naïve or resting anti-idiotypic T cells demonstrated the induction of anergy or apoptosis in the idiotypic T cell [61]. Analogous with such immune inhibition by anti-idiotypic responses, it has been shown in autoimmune diseases that it is not the presence of the autoantibody against self-proteins, but the lack of Ab2 which is the underlying characteristic amongst patients [67,68].

Hypotheses concerning the maintenance of immune memory without the presence of Ags have been proposed. UytdeHaag and colleagues first established that $CD5^+$ B lymphocytes could be activated by increases in CDR epitopes, derived from the expansion of Ag-specific B memory cells [69]. Theses $CD5^+$ B lymphocytes may undergo affinity maturation to increase affinity to the Ag-specific B cell idiotype, then, after Ag clearance the V region of the anti-idiotype $CD5^+$ B lymphocyte may serve as an Ag mimic to maintain memory cells [69]. Another hypothesis suggests that memory responses could be maintained, not only in the absence of persisting Ag, but also without long living memory cells. The interaction of idiotypic and anti-idiotypic responses could be an indefinite interaction, with no need for long-living memory B cells [70]. The same group found that peptidomimetics of the antigen in V regions of Ab2 are recognized by antigen-specific T cells and that maintenance of memory by the idiotype-anti-idiotype network could be extended to T cells as well [71]. The previous hypotheses agree with the need to generate T cell responses to help to achieve and regulate memory responses; furthermore, they propose mechanisms for affinity maturation based on idiotype-anti-idiotype interactions. Experimental designs and more importantly, results to confirm these hypotheses will be difficult to obtain but we cannot discard this phenomenon as a possible mechanism for immune memory maintenance [72].

5. Conclusions

We believe that along with the already well-known functions of Abs, TCRs and MHC molecules there are still several not fully appreciated nor completely understood but related immunological phenomena. Interactions established by these molecules could expand our understanding of the immune system by adding non-canonical immune functions to already well-known molecules. Of interest, is the possibility to explore the immunogenicity of Ig superfamily members, as a promising way to find novel molecular vaccine candidates. Furthermore, we believe that the "internal image" of an originally encountered Ag, represented by a collection of polyclonal Ab2 molecules, may potentially bear resemblance to an even larger pool of epitopes/mimotopes, present within pathogens or cancer cells; these may possibly reflect their entire antigenic landscape. If this is true, then it could aid in the development of much needed vaccines against antigenically variable pathogens and cancer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] K. Natarajan, M.G. Mage, D.H. Margulies, Immunoglobulin Superfamily, in: eLS, John Wiley & Sons Ltd, Chichester, 2015, pp. 1–7, https://doi.org/10.1002/9780470015902.a0000926.pub2.
[2] J.E. Slansky, K.R. Jordan, The Goldilocks model for TCR-too much attraction might not be best for vaccine design, PLoS Biol. 8 (2010) 1–5, https://doi.org/10.1371/journal.pbio.1000482.
[3] P. Chames, M. Van Regenmortel, E. Weiss, D. Baty, Therapeutic antibodies: successes, limitations and hopes for the future, Br. J. Pharmacol. 157 (2009) 220–233, https://doi.org/10.1111/j.1476-5381.2009.00190.x.
[4] D.M. Ecker, S.D. Jones, H.L. Levine, The therapeutic monoclonal antibody market, mAbs 7 (2015) 9–14. https://doi.org/ 10.4161/19420862.2015.989042.
[5] N. Landolina, F. Levi-Schaffer, Monoclonal antibodies: the new magic bullets for allergy: IUPHAR Review 17, Br. J. Pharmacol. 173 (2016) 793–803, https://doi.org/10.1111/bph.13396.
[6] K. Manoutcharian, R. Perez-Garmendia, G. Gevorkian, Recombinant antibody fragments for neurodegenerative diseases, Curr. Neuropharmacol. 15 (2017) 779–788, https://doi.org/10.2174/1570159x01666160930121647.
[7] L.M. Walker, D.R. Burton, Passive immunotherapy of viral infections: "super-antibodies" enter the fray, Nat. Rev. Immunol. 18 (2018) 297–308, https://doi.org/10.1038/nri.2017.148.
[8] M. Suzuki, C. Kato, A. Kato, Therapeutic antibodies: their mechanisms of action and the pathological findings they induce in toxicity studies, J. Toxicol. Pathol. 28 (2015) 133–139, https://doi.org/10.1293/tox.2015-0031.
[9] T. Te Wu, E.A. Kabat, An analysis of the sequences of the variable regions of Bence Jones proteins and myeloma light chains and their implications for antibody complementarity, J. Exp. Med. 132 (1970) 211–250, https://doi.org/10.1084/jem.132.2.211.
[10] H. Kohler, A. Pashov, T. Kieber-Emmons, The promise of anti-idiotype revisited, Front. Immunol. 10 (2019) 1–7, https://doi.org/10.3389/fimmu.2019.00808.
[11] J. Xu, X.J. Zhu, Y.H. Li, Y. Dai, Y.C. Zhu, et al., Expression, characterization and therapeutic efficacy of chimeric Fab of anti-idiotypic antibody NP30 against Schistosoma japonicum, Acta Trop. 118 (2011) 159–164, https://doi.org/10.1016/j.actatropica.2011.01.006.
[12] T. Dockree, C.J. Holland, M. Clement, K. Ladell, J.E. McLaren, et al., CD8 + T-cell specificity is compromised at a defined MHCI/CD8 affinity threshold, Immunol. Cell Biol. 95 (2017) 68–76, https://doi.org/10.1038/icb.2016.85.
[13] M.N. Artyomov, M. Lis, S. Devadas, M.M. Davis, A.K. Chakraborty, CD4 and CD8 binding to MHC molecules primarily acts to enhance Lck delivery, Proc. Natl. Acad. Sci. USA 107 (2010) 16916–16921, https://doi.org/10.1073/pnas.1010568107.
[14] J.S. Bridgeman, A.K. Sewell, J.J. Miles, D.A. Price, D.K. Cole, Structural and biophysical determinants of αβ T-cell antigen recognition, Immunology 135 (2011) 9–18, https://doi.org/10.1111/j.1365-2567.2011.03515.x.
[15] B.C. Sim, L. Zerva, M.I. Greene, N.R.J. Gascoigne, Control of MHC restriction by TCR V_α CDRI and CDR2, Science 273 (1996) 6–9, https://doi.org/10.1126/science.273.5277.963.
[16] K. Gao, L. Chen, Y. Zhang, Y. Zhao, Z. Wan, et al., Germline-encoded TCR-MHC contacts promote TCR V gene bias in umbilical cord blood T cell repertoire, Front. Immunol. 10 (2019) 1–12, https://doi.org/10.3389/fimmu.2019.02064.
[17] N.L. La Gruta, S. Gras, S.R. Daley, P.G. Thomas, J. Rossjohn, Understanding the drivers of MHC restriction of T cell receptors, Nat. Rev. Immunol. 18 (2018) 467–478, https://doi.org/10.1038/s41577-018-0007-5.
[18] A.S. Chong, D.M. Rothstein, K. Safa, L.V. Riella, Outstanding questions in transplantation: B cells, alloantibodies, and humoral rejection, Am. J. Transplant. 19 (2019) 2155–2163, https://doi.org/10.1111/ajt.15323.
[19] A. Loupy, C. Lefaucheur, Antibody-mediated rejection of solid-organ allografts, N. Engl. J. Med. 379 (2018) 2579–2582, https://doi.org/10.1056/NEJMra1802677.
[20] Y. Bouatou, D. Viglietti, D. Pievani, K. Louis, J.P. Doung Van Huyen, et al., Response to treatment and long-term outcomes in kidney transplant recipients with acute T cell–mediated rejection, Am. J. Transplant. 19 (2019) 1972–1988, https://doi.org/10.1111/ajt.15299.
[21] J.H.Y. Siua, R. Motallebzadehb, G.J. Pettigrewa, Humoral autoimmunity after solid organ transplantation: germinal ideas may not be natural, Cell. Immunol. 354 (2020) 1–16, https://doi.org/10.1016/j.cellimm.2020.104131.
[22] R. Marty, S. Kaabinejadian, D. Rossell, M.J. Slifker, J. van de Haar, et al., MHC-I genotype restricts the oncogenic mutational landscape, Cell 171 (2017) 1272–1283.e15, https://doi.org/10.1016/j.cell.2017.09.050.
[23] N. McGranahan, R. Rosenthal, C.T. Hiley, A.J. Rowan, T.B.K. Watkins, et al., Allele-specific HLA loss and immune escape in lung cancer evolution, Cell 171 (2017) 1259–1271.e11, https://doi.org/10.1016/j.cell.2017.10.001.
[24] R. Servín-Blanco, R.M. Chávaro-Ortiz, R. Zamora-Alvarado, F. Martínez-Cortes, G. Gevorkian, et al., Generation of cancer vaccine immunogens derived from major

histocompatibility complex (MHC) class I molecules using variable epitope libraries, Immunol. Lett. 204 (2018) 47–54, https://doi.org/10.1016/j.imlet.2018.10.008.
[25] M.K. Lemberg, F.A. Bland, A. Weihofen, V.M. Braud, B. Martoglio, Intramembrane proteolysis of signal peptides: an essential step in the generation of HLA-E epitopes, J. Immunol. 167 (2001) 6441–6446, https://doi.org/10.4049/jimmunol.167.11.6441.
[26] H. Wada, N. Matsumoto, K. Maenaka, K. Suzuki, K. Yamamoto, The inhibitory NK cell receptor CD94/NKG2A and the activating receptor CD94/NKG2C bind the top of HLA-E through mostly shared but partly distinct sets of HLA-E residues, Eur. J. Immunol. 34 (2004) 81–90, https://doi.org/10.1002/eji.200324432.
[27] J. Eugène, N. Jouand, K. Ducoin, D. Dansette, R. Oger, et al., The inhibitory receptor CD94/NKG2A on CD8$^+$ tumor-infiltrating lymphocytes in colorectal cancer: a promising new druggable immune checkpoint in the context of HLAE/β2m overexpression, Mod. Pathol. 33 (2020) 468–482, https://doi.org/10.1038/s41379-019-0322-9.
[28] S. Sivori, P. Vacca, G. Del Zotto, E. Munari, M.C. Mingari, et al., Human NK cells: surface receptors, inhibitory checkpoints, and translational applications, Cell. Mol. Immunol. 16 (2019) 430–441, https://doi.org/10.1038/s41423-019-0206-4.
[29] G. Goldstein, A.J. Fuccello, D.J. Norman, C.F. Shield III, R.B. Colvin, et al., OKT3 monoclonal antibody plasma levels during therapy and the subsequent development of host antibodies to OKT3, Transplantation 42 (1986) 507–511, https://doi.org/10.1097/00007890-198611000-00013.
[30] C. Sgro, Side-effects of a monoclonal antibody, muromonab CD3/orthoclone OKT3: bibliographic review, Toxicology 105 (1995) 23–29, https://doi.org/10.1016/0300-483x(95)03123-w.
[31] G. Salles, M. Barrett, R. Foà, J. Maurer, S. O'Brien, et al., Rituximab in B-cell hematologic malignancies: a review of 20 years of clinical experience, Adv. Ther. 34 (2017) 2232–2273, https://doi.org/10.1007/s12325-017-0612-x.
[32] Y.H. Ahn, H.G. Kang, J.M. Lee, H.J. Choi, I.S. Ha, et al., Development of antirituximab antibodies in children with nephrotic syndrome, Pediatr. Nephrol. 29 (2014) 1461–1464, https://doi.org/10.1007/s00467-014-2794-7.
[33] J.C. Almagro, T.R. Daniels-Wells, S.M. Perez-Tapia, M.L. Penichet, Progress and challenges in the design and clinical development of antibodies for cancer therapy, Front. Immunol. 8 (2018) 1–19, https://doi.org/10.3389/fimmu.2017.01751.
[34] S.M. Mahler, C.P. Marquis, G. Brown, A. Roberts, H.R. Hoogenboom, Cloning and expression of human V-genes derived from phage display libraries as fully assembled human anti-TNFα monoclonal antibodies, Immunotechnology 3 (1997) 31–43, https://doi.org/10.1016/s1380-2933(96)00058-9.
[35] N.K. Bender, C.E. Heilig, B. Dröll, J. Wohlgemuth, F.P. Armbruster, et al., Immunogenicity, efficacy and adverse events of adalimumab in RA patients, Rheumatol. Int. 27 (2007) 269–274, https://doi.org/10.1007/s00296-006-0183-7.
[36] F.A. Harding, M.M. Stickler, J. Razo, R. DuBridge, The immunogenicity of humanized and fully human antibodies: residual immunogenicity resides in the CDR regions, MAbs 2 (2010) 256–265, https://doi.org/10.4161/mabs.2.3.11641.
[37] A. Cassotta, V. Mikol, T. Bertrand, S. Pouzieux, J. Le Parc, et al., A single T cell epitope drives the neutralizing anti-drug antibody response to natalizumab in multiple sclerosis patients, Nat. Med. 25 (2019) 1402–1407, https://doi.org/10.1038/s41591-019-0568-2.
[38] M. Zanetti, Antigenized antibodies, Nature 355 (1992) 476–477, https://doi.org/10.1038/355476a0.
[39] R. Billetta, M.R. Hollingdale, M. Zanetti, Immunogenicity of an engineered internal image antibody, Proc. Natl. Acad. Sci. USA 88 (1991) 4713–4717, https://doi.org/10.1073/pnas.88.11.4713.
[40] H. Zaghouani, M. Krystal, H. Kuzu, T. Moran, H. Shah, et al., Cells expressing an H chain Ig gene carrying a viral T cell epitope are lysed by specific cytolytic T cells, J. Immunol. 148 (1992) 3604–3609.
[41] R. Billetta, G. Filaci, M. Zanetti, Major histocompatibility complex class I-restricted presentation of influenza virus nucleoprotein peptide by B lymphoma cells harboring an antibody gene antigenized with the virus peptide, Eur. J. Immunol. 25 (1995) 776–783, https://doi.org/10.1002/eji.1830250323.
[42] P.M. Patel, C.H. Ottensmeier, C. Mulatero, P. Lorigan, et al., Targeting gp100 and TRP-2 with a DNA vaccine: Incorporating T cell epitopes with a human IgG1 antibody induces potent T cell responses that are associated with favourable clinical outcome in a phase I/II trial, OncoImmunology 7 (2018) e1433516, https://doi.org/10.1080/2162402X.2018.1433516.
[43] K. Manoutcharian, L.I. Terrazas, G. Gevorkian, G. Acero, P. Petrossian, et al., Phage-displayed T-cell epitope grafted into immunoglobulin heavy-chain complementarity-determining regions: an effective vaccine design tested in murine cysticercosis, Infect. Immun. 67 (1999) 4764–4770.
[44] C. Pedroza-Roldan, C. Charles-Niño, R. Saavedra, T. Govezensky, L. Vaca, et al., Variable epitope library-based vaccines: shooting moving targets, Mol. Immunol. 47 (2009) 270–282, https://doi.org/10.1016/j.molimm.2009.09.024.
[45] C. Charles-Niño, C. Pedroza-Roldan, M. Viveros, G. Gevorkian, K. Manoutcharian, Variable epitope libraries: new vaccine immunogens capable of inducing broad human immunodeficiency virus type 1-neutralizing antibody response, Vaccine 29 (2011) 5313–5321, https://doi.org/10.1016/j.vaccine.2011.05.007.
[46] A. NoeDominguez-Romero, R. Zamora-Alvarado, R. Servín-Blanco, E.G. Perez-Hernández, L.E. Castrillon-Rivera, et al., Variable epitope library carrying heavily mutated survivin-derived CTL epitope variants as a new class of efficient vaccine immunogen tested in a mouse model of breast cancer, Hum. Vaccines Immunother. 10 (2014) 3201–3213, https://doi.org/10.4161/hv.29679.
[47] R. Bajwa, A. Cheema, T. Khan, A. Amirpour, A. Paul, et al., Adverse effects of immune checkpoint inhibitors (Programmed Death-1 inhibitors and cytotoxic T-lymphocyte-associated protein-4 Inhibitors): results of a retrospective study, J. Clin. Med. Res. 11 (2019) 225–236. https://doi.org/10.14740/jocmr3750.
[48] M. Ramos-Casals, J.R. Brahmer, M.K. Callahan, A. Flores-Chávez, N. Keegan, et al., Immune-related adverse events of checkpoint inhibitors, Nat. Rev. Dis. Prim. 6 (2020) 1–21, https://doi.org/10.1038/s41572-020-0160-6.
[49] A. Saha, S.K. Chatterjee, K.A. Foon, F.J. Primus, M. Bhattacharya-Chatterjee, Murine dendritic cells pulsed with an anti-idiotype antibody induce antigen-specific protective antitumor immunity, Cancer Res. 63 (2003) 2844–2854.
[50] A. Saha, S.K. Chatterjee, K.A. Foon, F.J. Primus, S. Sreedharan, et al., Dendritic cells pulsed with an anti-idiotype antibody mimicking carcinoembryonic antigen (CEA) can reverse immunological tolerance to CEA and induce antitumor immunity in CEA transgenic mice, Cancer Res. 64 (2004) 4995–5003.
[51] S. Alfonso, A. Valdés-Zayas, E.R. Santiesteban, Y.I. Flores, F. Areces, et al., A randomized, multicenter, placebo-controlled clinical trial of racotumomab-alum vaccine as switch maintenance therapy in advanced non-small cell lung cancer patients, Clin. Cancer Res. 20 (2014) 3660–3671, https://doi.org/10.1158/1078-0432.CCR-13-1674.
[52] V.G. Hemming, Use of intravenous immunoglobulins for prophylaxis or treatment of infectious diseases, Clin. Diagn. Lab. Immunol. 8 (2001) 859–863, https://doi.org/10.1128/CDLI.8.5.859.
[53] M.C. Dalakas, I. Illa, J.M. Dambrosia, S.A. Soueidan, D.P. Stein, et al., A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis, N. Engl. J. Med. 329 (1991) 1993–2000, https://doi.org/10.1056/NEJM199309303291401.
[54] R.A.C. Hughes, A.V. Swan, P.A. van Doorn, Intravenous immunoglobulin for Guillain-Barré syndrome, Cochrane Database Syst. Rev. (2012) 1–61, https://doi.org/10.1002/14651858.CD002063.pub5.
[55] L. Verdoni, A. Mazza, A. Gervasoni, L. Martelli, M. Ruggeri, et al., An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study, Lancet 6736 (2020) 1–8, https://doi.org/10.1016/s0140-6736(20)31103-x.
[56] S. Jolles, W.A.C. Sewell, S.A. Misbah, Clinical uses of intravenous immunoglobulin, Clin. Exp. Immunol. 142 (2005) 1–11, https://doi.org/10.1111/j.1365-2249.2005.02834.x.
[57] A. Matucci, E. Maggi, A. Vultaggio, Mechanisms of action of Ig preparations: immunomodulatory and anti-inflammatory effects, Front. Immunol. 5 (2015) 1–5, https://doi.org/10.3389/fimmu.2014.00690.
[58] A.S. De Groot, L. Moise, J.A. McMurry, E. Wambre, L. Van Overtvelt, et al., Activation of natural regulatory T cells by IgG Fc-derived peptide "Tregitopes", Blood 112 (2008) 3303–3311, https://doi.org/10.1182/blood-2008-02-138073.
[59] R.S. Blumberg, D. Lillicrap, IgG Fc immune tolerance group, tolerogenic properties of the Fc portion of IgG and its relevance to the treatment and management of hemophilia, Blood 131 (2018) 2205–2214, https://doi.org/10.1182/blood-2017-12-822908.
[60] G. Lal, M.S. Shaila, R. Nayak, Idiotypic T cells specific for Morbillivirus nucleocapsid protein process and present their TCR to cognate anti-idiotypic CD8$^+$ T cells, Immunol. Lett. 102 (2006) 132–140, https://doi.org/10.1016/j.imlet.2005.08.007.
[61] G. Lal, M.S. Shaila, R. Nayak, Activated mouse T cells downregulate, process and present their surface TCR to cognate anti-idiotypic CD4$^+$ T cells, Immunol. Cell Biol. 84 (2006) 145–153, https://doi.org/10.1111/j.1440-1711.2005.01405.x.
[62] A.J. Zajac, J.N. Blattman, K. Murali-Krishna, D.J.D. Sourdive, et al., Viral immune evasion due to persistence of activated T cells without effector function, J. Exp. Med. 188 (1998) 2205–2213, https://doi.org/10.1084/jem.188.12.2205.
[63] A. Gallimore, A. Glithero, A. Godkin, A.C. Tissot, A. Plückthun, et al., Induction and exhaustion of lymphocytic Choriomeningitis virus-specific cytotoxic T lymphocytes visualized using soluble tetrameric Major Histocompatibility Complex class I-peptide complexes, J. Exp. Med. 187 (1998) 1383–1393, https://doi.org/10.1084/jem.187.9.1383.
[64] E. Stronen, M. Toebes, S. Kelderman, M.M. van Buuren, W. Yang, et al., Targeting of cancer neoantigens with donor-derived T cell receptor repertoires, Science 352 (2016) 1337–1341, https://doi.org/10.1126/science.aaf2288.
[65] D.A. Hart, A.L. Wang, L.L. Pawlak, A. Nisonoff, Suppression of idiotypic specificities in adult mice by administration of antiidiotypic antibody, J. Exp. Med. 135 (1972) 1293–1300, https://doi.org/10.1084/jem.135.6.1293.
[66] H. Cosenza, H. Köhler, Specific inhibition of plaque formation to phosphorylcholine by antibody against antibody, Science 176 (1972) 1027–1029, https://doi.org/10.1126/science.176.4038.1027.
[67] S. Oak, L.K. Gilliam, M. Landin-Olsson, C. Törn, I. Kockum, et al., The lack of anti-idiotypic antibodies, not the presence of the corresponding autoantibodies to glutamate decarboxylase, defines type 1 diabetes, Proc. Natl. Acad. Sci. USA 105 (2008) 5471–5476, https://doi.org/10.1073/pnas.0800578105.
[68] Z.J. Pan, C.J. Anderson, H.A. Stafford, Anti-idiotypic antibodies prevent the serologic detection of antiribosomal P autoantibodies in healthy adults, J. Clin. Invest. 102 (1998) 215–222, https://doi.org/10.1172/JCI1969.
[69] F. Uytdehaag, R. van der Heijden, A. Osterhaus, Maintenance of immunological memory: a role for CD5$^+$ B cells? Immunol. Today. 12 (1991) 439–442, https://doi.org/10.1016/0167-5699(91)90016-M.
[70] R. Nayak, S. Mitra-Kaushik, M.S. Shaila, Perpetuation of immunological memory: a relay hypothesis, Immunology 102 (2001) 387–395, https://doi.org/10.1046/j.1365-2567.2001.01205.x.
[71] J. Vani, R. Nayak, M.S. Shaila, A CD8$^+$ T cell clone specific for antigen also recognizes peptidomimics present in anti-idiotypic antibody: implications for T cell memory, Cell. Immunol. 246 (2007) 17–25, https://doi.org/10.1016/j.cellimm.2007.05.001.
[72] J. Vani, R. Nayak, M.S. Shaila, Maintenance of antigen-specific immunological memory through variable regions of heavy and light chains of anti-idiotypic

antibody, Immunology 120 (2007) 486–496, https://doi.org/10.1111/j.1365-2567.2006.02519.x.