Università degli Studi di Padova

Padua Research Archive - Institutional Repository

Reverse immunoediting: When immunity is edited by antigen

Original Citation:

Availability:

This version is available at: 11577/3192459 since: 2016-07-11T17:49:14Z

Publisher:

Elsevier

Published version:

DOI: 10.1016/j.imlet.2016.04.015

Terms of use:

Open Access

This article is made available under terms and conditions applicable to Open Access Guidelines, as described at <http://www.unipd.it/download/file/fid/55401> (Italian only)

(Article begins on next page)

Accepted Manuscript

Title: Reverse immunoediting: when immunity is edited by Antigen

Author: Merlo Anna Dalla Santa Silvia Dolcetti Riccardo
Paola Zanovello Rosato Antonio

PII: S0165-2478(16)30066-9
DOI: <http://dx.doi.org/doi:10.1016/j.imlet.2016.04.015>
Reference: IMLET 5861

To appear in: *Immunology Letters*

Received date: 4-3-2016
Accepted date: 22-4-2016

Please cite this article as: Anna Merlo, Silvia Dalla Santa, Riccardo Dolcetti, Zanovello Paola, Antonio Rosato. Reverse immunoediting: when immunity is edited by Antigen. *Immunology Letters* <http://dx.doi.org/10.1016/j.imlet.2016.04.015>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Reverse immunoediting: when immunity is edited by Antigen

Merlo Anna^{a,1}, Dalla Santa Silvia^{b,1}, Dolcetti Riccardo^{c,d}, Paola Zanovello^{a,b}, Rosato Antonio^{a,bl,*}

^aVeneto Institute of Oncology IOV - IRCCS, Via Gattamelata, 64, 35128 Padua, Italy

^bDepartment of Surgery, Oncology and Gastroenterology, Via Gattamelata, 64, University of Padua, 35128 Padua

^cCRO-IRCCS, National Cancer Institute, Via F. Gallini, 2, 33081 Aviano, PN, Italy

^dUniversity of Queensland Diamantina Institute, Translational Research Institute, Brisbane, Queensland 4102, Australia

¹ These authors contributed equally to the work.

*Corresponding Author at: Department of Surgery, Oncology and Gastroenterology, University of Padua, Via Gattamelata 64, I-35128 Padua, Italy.

E-mail address: antonio.rosato@unipd.it

Tel: +39-049-8215858

Fax: +39-049-8072854

Disclosure of potential conflicts of interest: The authors declare that they have no conflict of interest.

Highlights

1. The immune response sculpts tumor features through the immunoediting process.
2. In “reverse immunoediting”, a tumor or a foreign antigen shapes the immune response.
3. Antigen load may be the key to expand or delete responding T cells.

Abstract

Immune selective pressure occurring during cancer immunoediting shapes tumor features revealed at clinical presentation. However, in the “Escape” phase, the tumor itself has the chance to influence the immunological response. Therefore, the capacity of the immune response to sculpt the tumor characteristics is only one side of the coin and even the opposite is likely true, i.e. that an antigen can shape the immune response in a sort of “reverse immunoediting”.

This reciprocal modeling probably occurs continuously, whenever the immune system encounters a tumor/foreign antigen, and can be operative in the pathogen/immune system interplay, thus possibly permeating the protective immunity as a whole. In line with this view, the characterization of a T cell response as well as the design of both active and passive immunotherapy strategies should also take into account all Ag features (type, load and presentation).

Overall, we suggest that the “reverse immunoediting” hypothesis could help to dissect the complex interplay between antigens and the immune repertoire, and to improve the outcome of immunotherapeutic approaches, where T cell responses are manipulated and reprogrammed.

Abbreviations

ACT, adoptive cell therapy; AICD, activation-induced cell death; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CAR, Chimeric Antigen Receptor; CIK, cytokine-induced killer; CML, chronic myeloid leukemia; CMV, Cytomegalovirus; CTL, cytotoxic T lymphocyte; EBV, Epstein-Barr virus; HIV, immunodeficiency virus; IAV, Influenza A virus; ID, immunodominance; IM, mononucleosis infection; LCMV, lymphocytic choriomeningitis virus; PAMP, pathogen-associated molecular pattern; PRAME, preferentially expressed antigen of melanoma; SCFA, short-chain fatty acid; TCR, T-Cell Receptor; TMEV, Theiler’s murine encephalomyelitis virus.

Keywords: immunotherapy; immunoediting; antigen; immunodominance; virus; cancer.

1. Introduction: from immunoediting to “reverse immunoediting”

Cancer immunoediting is a multi-faceted process that encompasses the well-known three Es, namely Elimination, Equilibrium and Escape [1]. Both adaptive and innate immunity cooperate in this process, and are more than sentinels with respect to nascent tumors. On the one hand, the immune system keeps under continuous selective pressure tumors that successfully elude immunosurveillance. On the other hand, during the equilibrium phase, it sculpts the characteristics of those tumors that ultimately become clinically evident. Quite paradoxically, the immune system promotes the growth of tumors that are subsequently less susceptible to a further immune attack. “Escaped” tumors in fact turn out to be poorly immunogenic due to the loss/reduction of strong tumor antigen, MHC, and co-stimulatory molecules expression. However, tumor cells do not passively submit to the action of immune cells, but actively counterattack by creating an immunosuppressive microenvironment. Indeed, the third E endorses the concept that also the tumor can interfere with the evolution of the specific immune response.

We reasoned that this concept of "reverse immunoediting" can also hold true for pathogens-immune system interplay, thus possibly permeating the immune response/repertoire as a whole.

2. The “reverse immunoediting”

2.1 How viruses can sculpture the immune response

The idea of “reverse immunoediting” firstly stemmed from the analysis of immunodominance (ID) in a retrovirus-induced tumor model [2]. In this study, we observed an unexpected immunodominance hierarchy in favor of lower avidity responding T cells (Fig. 1). An overwhelming antigen load indeed restrained and opposed the expansion of high avidity responding T cells through an activation-induced cell death (AICD) process

This particular mechanism of "reverse immunoediting", where the Ag load expands the best-fitting cell subsets and/or deletes higher functional avidity ones, can also be operative in other viral infection contexts and primarily under conditions of Ag persistence and/or high Ag load.

In this regard, during the course of the immune response against lymphocytic choriomeningitis virus (LCMV), changes in Ag load are coupled by modifications in the ID hierarchy as well as in the functional avidities of GP₃₃- and NP₃₉₆-specific cytotoxic T lymphocytes (CTLs) [3]. In particular, we speculate that the high and narrow range of functional avidity displayed by GP₃₃-specific CTLs condemn them to AICD in response to high viral load in the acute phase. Conversely, NP₃₉₆-specific CTLs that present a wider range of avidity can instead adapt to Ag load changes, and activation-induced apoptosis affects them likely to a lesser extent.

In the context of Influenza A virus (IAV) infection, variations in the ID hierarchy [4,5] can be partially ascribed to differential presentation levels of NP₃₆₆ and PA₂₂₄ viral epitopes, as T cell avidity in both responding populations is the same. Indeed, PA₂₂₄ turned out to be presented far less efficiently than NP₃₆₆ [5] and only by dendritic cells, while NP₃₆₆ is expressed on the surface of different cell types [4]. Therefore, NP₃₆₆-specific CTLs would be more prone to AICD than the PA₂₂₄-specific counterparts at high viral loads, and remain subdominant until the drop of viral load. With regard to human immunodeficiency virus (HIV), Lichterfeld M et al [6] demonstrated that higher viral loads are associated with a more pronounced decrease in functional avidity of Ag-specific T cells, and with a deletion of the majority of V β -specific subpopulations elicited in the acute phase. This deletion preferentially affects the subpopulations characterized by higher functional avidity in patients with high viral load, and can be due to a greater susceptibility to AICD in response to an excessive and chronic stimulation.

Similarly, during infection with Theiler's murine encephalomyelitis virus (TMEV), CD8⁺ T cells characterized by a moderate functional avidity are preferentially retained at the site of central nervous system infection. Indeed, the continuous viral antigenic stimulation induces a higher rate of AICD in T cells with high affinity, while providing low-avidity T cells with a survival advantage [7].

In the setting of Epstein-Barr virus (EBV) infection, the relationship between avidity and EBV Ag load has been only marginally investigated so far. However, despite the fact that the ID hierarchies

tend to be maintained stable over time and are conserved across different HLA haplotypes [8], qualitative changes in responding T cells actually do occur, but primarily at the level of single EBV Ag-specific T cell populations. For example, the TCR (T-Cell receptor) V β usage of T cells responding to EBV lytic Ag varies even drastically over time, or during the differentiation from CD45RA⁻CD28⁺ to CD45RA⁺CD28⁻ subsets [9,10] respectively. However, a mechanism resembling the one we are proposing could explain the differences in avidity and CD8 dependency between CD8⁺ T cells specific for the EBV lytic protein BMLF1 and the cytomegalovirus (CMV) protein pp65 in healthy virus carriers [11]. Again, high levels of viremia during the acute phase of EBV infection are suggested to induce relatively lower avidity BMLF1-specific T cell responses during the chronic phase, a scenario completely different from that of the early phases of CMV infection [11]. Quite unexpectedly, during mononucleosis infection (IM) and in the aftermath, EBV-specific T cells (in particular those directed to lytic antigens) appear to be more represented in periphery than in tonsils, where the foci of virus replication reside and the Ag load is consistently higher for a longer time [12]. In contrast, the reverse is true in long-term virus carriers. While the expression kinetics of tissue homing molecules in tonsils is reported to parallel the presence of Ag-specific T cells [12], a mechanism involving the Ag load and AICD induction in responding T cells could provide an additional and tailored explanation for the findings described.

2.2 How tumors can sculpt/edit the specific immune response

As defined in the Escape phase of the immunoediting theory [1], the tumor may sculpt specific immune responses primarily by producing cytokines and other factors that recruit different cell populations, and create an immunosuppressive microenvironment.

However, the tumor can exert its influence also in an antigen-dependent way, thus recapitulating the mechanism of “reverse immunoediting” we propose. In particular, the selective deletion of high-avidity CTLs appears to be a common immune evasion strategy of leukemias and involves different Ag specificities. As observed for the first time by Molldrem and coworkers [13], PR1-specific

CTLs characterized by high-avidity were found in healthy donors and chronic myeloid leukemia (CML) patients in cytogenetic remission, but were absent in untreated patients with high tumor burden. Similarly, PR1-specific CTLs disappeared in concomitance with the relapse in CML patients, and reappeared after imatinib therapy in inverse proportion to the antigen transcript levels [14]. Conversely, these specific T cells are undetectable or barely identifiable in patients with constantly high tumor burdens (as assessed at a molecular and cytogenetic level).

Even with regard to the PRAME (preferentially expressed antigen of melanoma) antigen, an inverse correlation was found between the avidity of Ag-specific CTLs and the expression of the molecule in both acute lymphoblastic (ALL) or myeloid (AML) leukemia, and CML patients [15]. In line with these findings, Ag-specific CTLs isolated and expanded from CML patients with active disease were characterized by lower avidity for PRAME-derived peptides than CTLs from healthy donors [16].

2.3 The impact of reverse immunoediting on immunotherapy approaches

This new concept of “reverse immunoediting” points out that the characterization of a T cell response should also comprise the reality of Ag load and presentation. In particular, the mechanism we propose may have profound implications in the field of immunotherapy, where the researchers have the possibility to manipulate the T cell responses with transgenic TCR or Chimeric Antigen Receptors (CAR).

In this context, we suggest that the selection of the most avid CTL/TCR would not necessarily improve the therapeutic outcome, as their transfer in the presence of a high tumor burden could lead to a kind of unintended "immune kamikazing", as reported by others [17]. Indirectly, the same concept holds true even for CAR-transduced cells. Indeed, CAR with stronger signaling capacity for the addition of a third costimulatory moiety has been associated to a higher rate of AICD in transduced cytokine-induced killer (CIK) cells [18]. We speculate that the AICD resulting from an

excess of stimulation can in part explain those cases in which 2nd generation CAR-transduced T cells outperform 3rd generation counterparts [19].

Overall, we envisage that the search for the best immunotherapy strategy is strictly model-dependent, and should not disregard the power of antigen load encountered *in vivo* by T cells both in adoptive cell therapy (ACT) and in vaccination strategies. It is worth noting that in AML or MDS (myelodysplastic syndrome) patients vaccinated with the WT1 peptide, a significant increase in WT1-specific CD8⁺ T cells was documented only in patients with low leukemic blast counts in the bone marrow, as a proof of the "antigen-load" effect of the high leukemic burden [20]. In active immunotherapy, indirect evidence of this phenomenon could be inferred where no correlations are found between immune and clinical responses [21]. For example, in a vaccination protocol with gp100 peptide, the presence of antigen-specific CD8⁺ T cells in blood did not correlate with clinical benefit [22].

Moreover, therapeutic vaccination protocols inducing an excessive Ag presentation did not necessarily improve the natural response to the tumor. In a phase II clinical trial involving patients with myeloid malignancies, both high- and low-avidity PR1 and WT1-specific CD8⁺ T cells were transiently detected in all patients after the first vaccine dose, but repeated PR1 and WT1 peptide doses led to rapid loss of high-avidity Ag-specific T cells [21]. Similarly, analysis of gp100-specific memory CD8⁺ T cells in melanoma patients revealed that they did not acquire enhanced functional avidity after boosting immunization with peptide [23]. On the whole, active immunotherapy approaches that do not accurately take into account all of the factors impacting the fine balance between antigen and responding T cells cannot reach their goal or, in principle, can be even detrimental through the induction of immune tolerance/anergy/ignorance.

2.4 Broadening the horizons of “reverse immunoediting”

The immune system co-evolves with the type and burden of stimuli received, and the encounter with particular antigens/microorganisms can have profound influences/repercussions on human physiopathology.

Perhaps the most impressive example of this intimate relationship is the cohabitation of the intestinal microbiota and the immune system. The disequilibrium between the immune system and the “tolerated” trillions of bacteria, viruses, fungi and Archaea that greatly outnumber human cells in the body [24], potentially predisposes the host to different diseases such as allergies, asthma, inflammatory bowel disease, and cancer. While the influence of the microbiota on the immune system is mainly mediated by bacterial metabolism products (e.g. short-chain fatty acids, SCFA) or pathogen-associated molecular pattern (PAMPs) molecules, also a truly antigen-driven influence probably takes place. Classically, anti-A and anti-B naturally occurring antibodies are produced against terminal carbohydrates on bacterial cell wall of normal intestinal microbial flora. More recently, the mucosal Th17 cell differentiation was demonstrated to be driven by Segmented Filamentous Bacteria and mandatorily requires MHC-II presentation [25]. Such an antigen-driven influence can possibly be a common mechanism, since V(D)J recombination/receptor editing processes that occur also in B cells of gut lamina propria gives luminal antigens the opportunity to shape the pre-immune repertoire [26].

As another paradigmatic example, the T cell-mediated symptoms of IM afflicting especially adults and adolescents, are due to the larger T cell repertoires in adults than in children, which contain memory lymphocytes possibly cross-reacting against EBV antigens. One of such cross-reactivities involves influenza A virus M1 and EBV BMLF1 [27].

As a double-edged sword, TCR cross-reactivity equips the immune system with the robustness needed for responding to most novel pathogens, in particular after thymic involution [28], but on the other hand it may expose the host to the risk of an erroneous discrimination between self and non-self. Indeed, in genetically susceptible hosts, some pathogens harboring antigens that are very

similar but not identical to self-antigens can activate harmless autoreactive immune cells, leading to breakdown of self-tolerance and finally to autoimmune diseases. While well documented in some cases or only suggested, molecular mimicry is one of the mechanisms that creates a link between defined viruses, bacteria or parasites and autoimmune diseases; this is the case of Enteroviruses and type 1 diabetes mellitus, EBV and multiple sclerosis, *Streptococcus pyogenes* and rheumatic fever, *Trypanosoma cruzi* and Chagas disease [29], just to cite a few.

3. Conclusions

Evidence so far accumulated in various settings suggests that the global number of antigen-responding T cells can be considered simultaneously both the effect and the cause of the antigen load, because they proliferate in response to the cognate (pathogen or tumor) antigen, and at the same time their expansion and effector activity may restrict their own proliferation stimulus.

This apparently mere “number question” indeed influences not only the fate of an infection/evolution of a tumor, but also the overall quality of the immune response elicited. In fact, by modulating the pool of distinct immune cell subpopulations, an antigen can effectively shape the characteristics of the specific T cell response as a whole. This reciprocal modeling or Darwinian selection probably occurs continuously (Fig. 2), whenever the immune system encounters a tumor/foreign antigen.

In conclusion, we suggest that the capacity of the immune response to sculpt the tumor characteristics, as reported in the immunoediting theory, is only one side of the coin. Even the opposite is likely true, i.e. that an antigen can shape the immune response. This “reverse immunoediting” hypothesis could help to dissect the complexity of the intimate relationship between the antigens and the immune repertoire, and to improve the design of immunotherapeutic strategies.

Acknowledgments

This work was partly supported by grants from the Associazione Italiana per la Ricerca sul Cancro (AIRC, IG-17035; Special Program Molecular Clinical Oncology 5 per mille, ID 10016, and Progetto di Ricerca di Ateneo 2015).

References

- [1] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. *Current opinion in immunology*;27:16-25.
- [2] Dalla Santa S, Merlo A, Bobisse S, Ronconi E, Boldrin D, Milan G, Barbieri V, Marin O, Facchinetti A, Biasi G, Dolcetti R, Zanolello P, Rosato A. Functional avidity-driven activation-induced cell death shapes CTL immunodominance. *J Immunol*;193:4704-4711.
- [3] Raue HP, Slifka MK. CD8+ T cell immunodominance shifts during the early stages of acute LCMV infection independently from functional avidity maturation. *Virology* 2009;390:197-204.
- [4] Crowe SR, Turner SJ, Miller SC, Roberts AD, Rappolo RA, Doherty PC, Ely KH, Woodland DL. Differential antigen presentation regulates the changing patterns of CD8+ T cell immunodominance in primary and secondary influenza virus infections. *The Journal of experimental medicine* 2003;198:399-410.
- [5] Luciani F, Sanders MT, Oveissi S, Pang KC, Chen W. Increasing viral dose causes a reversal in CD8+ T cell immunodominance during primary influenza infection due to differences in antigen presentation, T cell avidity, and precursor numbers. *J Immunol* 2013;190:36-47.
- [6] Lichterfeld M, Yu XG, Mui SK, Williams KL, Trocha A, Brockman MA, Allgaier RL, Waring MT, Koibuchi T, Johnston MN, Cohen D, Allen TM, Rosenberg ES, Walker BD, Altfeld M. Selective depletion of high-avidity human immunodeficiency virus type 1 (HIV-1)-specific CD8+ T cells after early HIV-1 infection. *Journal of virology* 2007;81:4199-4214.
- [7] Kang HS, Kim BS. Predominant clonal accumulation of CD8+ T cells with moderate avidity in the central nervous systems of Theiler's virus-infected C57BL/6 mice. *Journal of virology*;84:2774-2786.
- [8] Hislop AD, Taylor GS, Sauce D, Rickinson AB. Cellular responses to viral infection in humans: lessons from Epstein-Barr virus. *Annual review of immunology* 2007;25:587-617.
- [9] Annels NE, Callan MF, Tan L, Rickinson AB. Changing patterns of dominant TCR usage with maturation of an EBV-specific cytotoxic T cell response. *J Immunol* 2000;165:4831-4841.
- [10] Iancu EM, Corthesy P, Baumgaertner P, Devedre E, Voelter V, Romero P, Speiser DE, Rufer N. Clonotype selection and composition of human CD8 T cells specific for persistent herpes viruses varies with differentiation but is stable over time. *J Immunol* 2009;183:319-331.
- [11] Price DA, Brenchley JM, Ruff LE, Betts MR, Hill BJ, Roederer M, Koup RA, Migueles SA, Gostick E, Wooldridge L, Sewell AK, Connors M, Douek DC. Avidity for antigen shapes clonal dominance in CD8+ T cell populations specific for persistent DNA viruses. *The Journal of experimental medicine* 2005;202:1349-1361.
- [12] Hislop AD, Kuo M, Drake-Lee AB, Akbar AN, Bergler W, Hammerschmitt N, Khan N, Palendira U, Leese AM, Timms JM, Bell AI, Buckley CD, Rickinson AB. Tonsillar homing of Epstein-Barr virus-specific CD8+ T cells and the virus-host balance. *The Journal of clinical investigation* 2005;115:2546-2555.
- [13] Molldrem JJ, Lee PP, Kant S, Wieder E, Jiang W, Lu S, Wang C, Davis MM. Chronic myelogenous leukemia shapes host immunity by selective deletion of high-avidity leukemia-specific T cells. *The Journal of clinical investigation* 2003;111:639-647.
- [14] Kanodia S, Wieder E, Lu S, Talpaz M, Alatrash G, Clise-Dwyer K, Molldrem JJ. PR1-specific T cells are associated with unmaintained cytogenetic remission of chronic myelogenous leukemia after interferon withdrawal. *PloS one*;5:e11770.

- [15] Rezvani K, Yong AS, Tawab A, Jafarpour B, Eniafe R, Mielke S, Savani BN, Keyvanfar K, Li Y, Kurlander R, Barrett AJ. Ex vivo characterization of polyclonal memory CD8+ T-cell responses to PRAME-specific peptides in patients with acute lymphoblastic leukemia and acute and chronic myeloid leukemia. *Blood* 2009;113:2245-2255.
- [16] Quintarelli C, Dotti G, De Angelis B, Hoyos V, Mims M, Luciano L, Heslop HE, Rooney CM, Pane F, Savoldo B. Cytotoxic T lymphocytes directed to the preferentially expressed antigen of melanoma (PRAME) target chronic myeloid leukemia. *Blood* 2008;112:1876-1885.
- [17] Chhabra A, Mukherji B. Death receptor-independent activation-induced cell death in human melanoma antigen-specific MHC class I-restricted TCR-engineered CD4 T cells. *J Immunol*;191:3471-3477.
- [18] Hombach AA, Rappl G, Abken H. Arming cytokine-induced killer cells with chimeric antigen receptors: CD28 outperforms combined CD28-OX40 "super-stimulation". *Mol Ther*;21:2268-2277.
- [19] Abate-Daga D, Lagisetty KH, Tran E, Zheng Z, Gattinoni L, Yu Z, Burns WR, Miermont AM, Teper Y, Rudloff U, Restifo NP, Feldman SA, Rosenberg SA, Morgan RA. A novel chimeric antigen receptor against prostate stem cell antigen mediates tumor destruction in a humanized mouse model of pancreatic cancer. *Human gene therapy*;25:1003-1012.
- [20] Keilholz U, Letsch A, Busse A, Asemisen AM, Bauer S, Blau IW, Hofmann WK, Uharek L, Thiel E, Scheibenbogen C. A clinical and immunologic phase 2 trial of Wilms tumor gene product 1 (WT1) peptide vaccination in patients with AML and MDS. *Blood* 2009;113:6541-6548.
- [21] Rezvani K, Yong AS, Mielke S, Jafarpour B, Savani BN, Le RQ, Eniafe R, Musse L, Boss C, Kurlander R, Barrett AJ. Repeated PR1 and WT1 peptide vaccination in Montanide-adjuvant fails to induce sustained high-avidity, epitope-specific CD8+ T cells in myeloid malignancies. *Haematologica*;96:432-440.
- [22] Sosman JA, Carrillo C, Urba WJ, Flaherty L, Atkins MB, Clark JI, Dutcher J, Margolin KA, Mier J, Gollob J, Kirkwood JM, Panka DJ, Crosby NA, O'Boyle K, LaFleur B, Ernstoff MS. Three phase II cytokine working group trials of gp100 (210M) peptide plus high-dose interleukin-2 in patients with HLA-A2-positive advanced melanoma. *J Clin Oncol* 2008;26:2292-2298.
- [23] Walker EB, Haley D, Petrausch U, Floyd K, Miller W, Sanjuan N, Alvord G, Fox BA, Urba WJ. Phenotype and functional characterization of long-term gp100-specific memory CD8+ T cells in disease-free melanoma patients before and after boosting immunization. *Clin Cancer Res* 2008;14:5270-5283.
- [24] Surana NK, Kasper DL. Deciphering the tete-a-tete between the microbiota and the immune system. *The Journal of clinical investigation*;124:4197-4203.
- [25] Goto Y, Panea C, Nakato G, Cebula A, Lee C, Diez MG, Laufer TM, Ignatowicz L, Ivanov, II. Segmented filamentous bacteria antigens presented by intestinal dendritic cells drive mucosal Th17 cell differentiation. *Immunity*;40:594-607.
- [26] Wesemann DR, Portuguese AJ, Meyers RM, Gallagher MP, Cluff-Jones K, Magee JM, Panchakshari RA, Rodig SJ, Kepler TB, Alt FW. Microbial colonization influences early B-lineage development in the gut lamina propria. *Nature*;501:112-115.
- [27] Clute SC, Watkin LB, Cornberg M, Naumov YN, Sullivan JL, Luzuriaga K, Welsh RM, Selin LK. Cross-reactive influenza virus-specific CD8+ T cells contribute to lymphoproliferation in Epstein-Barr virus-associated infectious mononucleosis. *The Journal of clinical investigation* 2005;115:3602-3612.
- [28] Petrova G, Ferrante A, Gorski J. Cross-reactivity of T cells and its role in the immune system. *Critical reviews in immunology*;32:349-372.
- [29] Kivity S, Agmon-Levin N, Blank M, Shoenfeld Y. Infections and autoimmunity--friends or foes? *Trends in immunology* 2009;30:409-414.

Figure Captions

Fig. 1. Potential mechanism of “reverse immunoediting”. A schematic model of the relationship between T cell functional avidity and antigen load in the establishment of the immunodominance hierarchy.

Fig. 2. The continuous process of reciprocal modeling between the antigen and the specific immune response, as exemplified in the famous lithograph “Drawing Hands” of Maurits Cornelis Escher (M.C. Escher’s “Drawing Hands” © 2015 The M.C. Escher Company - the Netherlands. All rights reserved. Used by permission. www.mcescher.com)