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Divergent roles of anti-self antibodies during infection

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Abstract

Anti-self antibodies are most commonly associated with auto-immune disorders, but a large body of evidence indicates that they are also present in numerous infectious diseases. These autoimmune antibodies appear transiently during infection with a number of viruses, bacteria and parasites, and in some cases, have been associated with the development of auto-immune disorders that develop after infection has been cleared. Traditionally these infection-associated auto-antibodies are considered an erroneous byproduct of a legitimate immune response, but their possible role in the clearance of microbes and infected cells or inhibition of host-cell invasion suggests that they may be present because of their beneficial protective role against different infections.

Anti-self antibodies are common during different infections and may have a protective role

Antibodies are an essential immune component mediating both clearance and control of infections. Anti-self antibodies, which recognize the host's own molecules and tissues, play a crucial role in the pathology of various autoimmune disorders such as systemic lupus erythematosus. Surprisingly, many infections have been linked to the development of autoimmune-like responses, particularly production of anti-self antibodies [1, 2]. Perhaps unsurprisingly, anti-self antibodies generated during infection can have an immediate pathological role, such as seen during Chikungunya virus infection or malaria, where they induce arthritis-like symptoms or anemia, respectively [3, 4]. Infections such as *Campylobacter jejuni* or Epstein Barr virus can also contribute to the development of chronic autoimmune disorders after infection [5, 6].

More recently however, anti-self antibodies have also been attributed a beneficial role in combating various infections. This dual role has led to investigate the question of whether the generation of anti-self antibodies during infection is consequential or an erroneous immune phenomenon. In this article, we will review recent evidence of autoimmune-like responses during various infections, as well as discuss different roles of anti-self antibodies during bacterial, viral and protozoan infections.

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Autoimmunity induced by bacterial infections

Bacterial infections, either acute or chronic, are frequent in humans, and include a large variety of species. Autoimmune-like responses have been reported in various types of bacterial infections. In many cases, the autoimmune response was proposed to be mediated by mechanisms such as molecular mimicry, where the bacteria carry antigens that are similar to the host's, inducing cross-reactive antibodies. Autoimmune-like responses during bacterial infections involve high levels of potentially pathological anti-self antibodies against various host molecules such as gangliosides, DNA or carbohydrate motifs. A classic example is the association between Guillain-Barré syndrome (GBS) and infection with the gastrointestinal pathogen *Campylobacter jejuni*. In this case, anti-self antibodies against lipooligosaccharides from the bacterium are generated which recognize gangliosides, such as GM1, due to their similar structure [7]. These antibodies recognize both bacterial molecules and gangliosides in human peripheral nerves, leading to neurological damage.

In the case of *Mycobacterium tuberculosis*, the causative agent of tuberculosis, antibodies that cross-react with mycobacterial cell wall glycolipids, DNA and host cardiolipin are found [8]. Since some lipids are shared between both humans and *M. tuberculosis*, it is possible that the high abundance of bacterial lipid antigen presentation results in cross-reactive antibodies [9]. Another interesting example is the development of rheumatic heart disease in association with *Streptococcus pyogenes* infection, where the bacterial antigen M protein resembles host heart muscle cell protein myosin [10]. Other examples include infections with Chlamydia and Campylobacter bacteria that lead to reactive arthritis [11]. The mechanism involving a post-infection autoimmune arthritis has been attributed to cross-reactivity of bacterial antigens with host joint tissues [11].

Interestingly, anti-self antibody generation during bacterial infection has been reported to be beneficial during *Streptococcus pneumoniae* infection, a major leading cause of mortality across the globe. Although this bacterium is a common member of the nasal microbiota, some strains can lead to a severe form disease. Naturally occurring IgM antibodies against phosphorylcholine cross-react with the same phospholipid on the surface of the bacterium hence promoting clearance and control of the infection [12].

Other natural antibodies against carbohydrate motifs, such as α -gal, are induced naturally as a response to the gut microbiota and can be increased upon specific bacterial infections. These antibodies confer resistance to malaria and possibly other infections [13].

Virus-induced autoimmunity

Viral infections represent a significant global burden of infectious diseases, and are also some of the most frequent infections humans face, such as the common cold or herpes virus infections. Virus-induced autoimmunity is a highly reported phenomenon in many different globally-relevant infections including HIV and Hepatitis viruses, and more recently as a response to emerging arboviruses. Some of the most reported autoimmune-like phenomena seen after viral infections include: thrombocytopenia, hemolytic anemia, anti-phospholipid syndrome and autoimmune arthritis [14–18].

The mechanisms underlying the production of anti-self antibodies during viral infections has been attributed to different processes, including: breaking of self-tolerance through infection of immune-regulatory cells (HIV infection of regulatory NKT cells), molecular mimicry, superantigens (that activate T cells without the need for antigen presentation), epitope spreading, and polyclonal and bystander activations [14, 19, 20]. This diversity in proposed mechanisms is mainly attributable to the fact that viral pathogens are intracellular, “parasitic”, and hijack the host molecules to their survival.

Epitope spreading and bystander activation are mainly mediated by highly inflammatory conditions frequently found in acute infections that allow the immune presentation of neo antigens made from host molecules, hence leading to the activation of self-reactive lymphocytes.

Chronic viral infections, such as HIV and viral hepatitis, have been more strongly associated with the emergence of autoimmune-like phenomena [21]. For example, such infections can lead to anti-phospholipid syndrome, which is characterized by the production anti-self phospholipid antibodies that contribute to the development of serious complications such as thrombocytopenia and anemia [22]. Other anti-self antibodies reported during chronic viral infections include anti-nuclear antibodies (ANAs) [23, 24].

Another group of viral infections that can lead to autoimmune-like pathologies are the emerging arboviruses Zika, Chikungunya and Dengue viruses. These viruses have been reported to lead to autoimmune-like pathologies including thrombocytopenia, GBS and autoimmune arthritis. The one that has received more attention from both the research community and general public has been the neurological complications associated with Zika infection, such as GBS [15]. Zika- associated neurological complications are probably related with the capacity of Zika to infect neural stem cells [25–27]. However, in addition to this, it has been proposed that the development of Zika-associated GBS may be caused by anti-self ganglioside antibodies generated during infection, highlighting a possible autoimmune-like component [28–30]. Indeed, high levels of anti-GD3 ganglioside antibodies are found in Zika patients [31]. Since Dengue and Chikungunya infections can also lead to auto-antibody production [17], it is possible that shared autoimmune triggers are present in these three infections. Chikungunya has been associated to transient autoimmune arthritis [3, 32], similar to the chronic autoimmune disorder rheumatoid arthritis (RA), which affects humans and is characterized by high production of anti-self antibodies that target proteins in the joints, such as citrullinated proteins [33, 34]. These antibodies have also been detected in Chikungunya infection [17], hence suggesting similar pathogenesis between Chikungunya and RA, although the viral infection triggers it only transiently.

In chronic autoimmune disorders like RA and lupus, freely available extracellular nucleic acids have been proposed to have a role in activating autoreactive B-cell clones [35, 36]. Since viruses are relatively simple pathogens composed in a large percentage by nucleic acids, which are potent immune activators (PAMPs), it has been proposed that similar autoimmune-like triggers are activated during some viral infections and autoimmune disorders. In accordance, recent studies have implicated T-bet⁺ B-cells, that expand both in viral infections and autoimmune disease mice models, as high producers of ANAs in both

scenarios [23, 37]. Collectively, these data suggest that there are shared autoreactive triggers between chronic autoimmune disorders and some viral infections.

Protozoan parasite driven autoimmune responses

Infectious parasitic protozoans are complex pathogens that represent some of the biggest challenges in global health. These relevant human parasitic pathogens include *Plasmodium*, *Trypanosoma* and *Toxoplasma*. Similarly to many viral infections, these parasitic protozoans establish chronic infections in their hosts, which has allowed them to co-evolve for thousands of years, shaping their host's genetics and possibly immune systems. Additionally, some of these relevant parasitic pathogens have been associated to the development of autoimmune-like pathologies during and even after infection, including: autoimmune anemia, thrombocytopenia and cardiac complications [4, 38–42]. The mechanisms by which parasitic protozoans lead to auto-reactivity are still not well understood. They could be similar to the ones proposed for viral infections, such as: epitope spreading, bystander activation, persistent infection and polyclonal activation. Nevertheless, since parasitic protozoans are genetically closer organisms to their hosts than bacterial and viral agents, they share a number of antigenic targets that could be sensed by the immune system and induce reactivity towards both parasite and host. This would imply that mechanisms involving shared antigenic targets would be the most frequent as origin for parasite-induced autoimmunity.

Malaria is a parasitic disease caused by *Plasmodium* parasites and transmitted through *Anopheles* mosquitoes. This infection is one of the most ancient reported diseases and still a major killer infectious disease in the world, with over 200 million new cases and close to 500,000 deaths last year [43]. Malaria parasites undergo a complex life cycle in their host, which includes an asymptomatic liver stage and an intracellular erythrocyte blood stage. All the complications associated with malaria have been reported to occur during the blood stage. *Plasmodium* parasites have greatly influenced human evolution inducing the selection of many genetic adaptations that are protective against malaria, which include the sickle cell anemia trait and the lack of Duffy antigen. Interestingly, malaria has been repeatedly reported to lead to autoimmune-like phenomena, mainly the development of autoantibodies [44]. Some of the self-antigens highly targeted during malaria infection include membrane phospholipids, nucleic acids and erythrocyte proteins. Even though autoimmunity during malaria is a highly reported phenomena, its role and mechanisms during the infection have not been thoroughly explored [45]. Anemia is a frequent complication of malaria that is not majoritarily caused by the loss of erythrocytes infected with *Plasmodium*, but by the loss of uninfected erythrocytes that are cleared during infection. Recently, a pathogenic role has been attributed to anti-self antibodies in malaria by mediating the clearance of uninfected erythrocytes during infection. The membrane phospholipid phosphatidylserine (PS) has been identified as a major target for autoantibodies generated during malaria. These antibodies recognize uninfected erythrocytes exposing PS on their surface, hence promoting malarial anemia in days of low or no parasitemia [4]. The autoreactive B-cell population expressing the transcription factor T-bet, already identified in some viral infections as producers of ANAs [23, 37], was identified as a major mediator of anti-PS auto-reactivity during malaria anemia. The *Plasmodium* parasite was attributed a direct role in activating these autoreactive

T-bet+ B-cells through parasite DNA activation [46]. Additionally, ANAs that have been extensively reported during malaria, are probably generated by a similar mechanism. Some reports have suggested ANAs as mediators in both protection and pathology in mice malaria models [47, 48]. Collectively, these reports confirm the importance of autoimmunity in the protection and pathology during malaria [45].

Other parasitic diseases that lead to autoimmune-like phenomena include the trypanosomatid parasites, such as *Trypanosoma cruzi* that causes Chagas disease. Particularly, antibodies against sugar moieties are abundantly generated during acute infection, persist during the chronic state, and were attributed to lead to the cardiac pathology seen during Chagas disease [42]. However, this hypothesis has been disfavored since the anti-parasitic treatment of chronically infected patients leads to improved clinical outcomes, suggesting that classical infection-induced cellular damage and inflammation were the cause of the pathology [49].

Lastly, *Toxoplasma gondii* is the parasitic agent that causes toxoplasmosis. This infection has been attributed to lead to arthritic, atopic, thyroid and other complications [1, 50]. Autoantibodies, such as ANAs, have also been reported during this infection and could be involved in mediating these autoimmune-like pathologies to some extent. Nevertheless, more mechanistic research is needed to move on from the reported correlations between *T. gondii* infection and autoimmune development.

Common mechanisms for classical and infection-induced autoimmunity?

Contrary to the conventional belief of a sharp differentiation of self and non-self antigens, reports for autoimmune antibodies are frequent for infectious diseases, regardless of the nature of the causative pathogen, as the examples above illustrate.

Recently, a similar mechanism for the generation of anti-self antibodies has been proposed for classic auto-immune diseases and microbial infections, which identifies the autoreactive B-cell population expressing the transcription factor T-bet as major producers of autoimmune antibodies. During infectious diseases such as malaria [46] and viruses such as herpes, lymphocytic choriomeningitis virus (LCMV), and vaccinia [19], as well as in classical auto-immune disorders, such as lupus [51], T-bet+ B-cells were found to be major producers of anti-self antibodies. Both in infectious and classical autoimmunity, the mechanisms of activation of T-bet+ B-cells for the generation of anti-self antibodies involves the recognition of a nucleic acid by a specific TLR in synergy with the activation of the inflammatory cytokine Interferon gamma receptor and the autoantigen [23, 37, 46, 51]. These recent findings suggest the possibility of shared mechanisms between classical and infectious autoimmunity, adding a possible explanation for the well-established relationship between some infections and the generation of autoimmune disorders, as described above.

Although the nature of the self antigens recognized by autoimmune-like antibodies is diverse, a general characteristic shared by infections with either bacteria, virus or parasites, is the generation of ANAs antibodies, which appear during acute infection and may remain at low levels during chronic infections [52]. Some of these ANAs antibodies can cross-react

with host specific proteins, glycolipids and proteoglycans, increasing the potential for autoimmune complications [8, 53].

A protective role for autoimmune antibodies during infection?

It should be considered that before the rise of autoimmune antibodies during infection, natural antibodies already represent the first line of defense against pathogens [54]. These natural antibodies are usually present in human serum and are generated in the absence of previous immune activation [55]. Natural antibodies are deemed as “natural” because they are present in the absence of previous antigen stimuli and do not require it for the clonal selection of these B cells during early development [52]. These natural antibodies in the steady state include usual natural IgM (and IgA) antibodies and have been described to be mainly produced by innate-like B1 lymphocytes [56]. Natural antibodies can recognize microbial antigens, but also self-antigens, such as phosphatidylcholine, a common membrane lipid, or CCR5, a chemokine receptor used by HIV for entry. Due to their crossreactive nature, these natural antibodies (such as the T15 idiotype antibody) have a protective role against certain bacterial infections and even against atherosclerotic plaques. Additionally they have a homeostatic role in clearing apoptotic and dying cells preventing auto-inflammatory immune responses [57]. In accordance, various studies have reported decreased levels of natural antibodies correlated with increased susceptibility to development of autoimmunity [58, 59]. Although having low affinity, these antibodies are thought to contribute to natural immunity in the protection against infections, already suggesting that autoimmune responses may have a beneficial protective component for the host [60].

The development of autoimmune-like conditions after different kinds of infections is a well-documented clinical problem. Frequently, autoimmune-like responses induced by infectious agents have been disregarded as ‘collateral damage’. They are considered erroneous due to molecular mimicry or cross-reactivity caused by greatly similar or shared pathogen molecules with the host. Although it is clear that they can have negative effects in disease pathology, anti- self antibodies induced by infections may also have beneficial protective effects for the host. It is possible that throughout evolution, the mechanism of producing anti-self antibodies in response to infections has been selected because it conferred an advantage against pathogens. In this case, the autoimmune pathology generated would be considered the ‘price to pay’ for enhanced immunity against infections. A possible example of these protective effects may be the rise of autoimmune anti-phospholipid cross-reactive antibodies during some infections [1, 4, 16, 61], since these phospholipids are present in viral capsids and are involved in virus entry [62–64]. It is also likely that anti-PS antibodies, that appear during multiple infections, recognize infected cells that expose this phospholipid upon being infected, targeting these cells for clearance [65, 66].

Concluding Remarks

Autoimmune-like responses during infection may have divergent roles depending on the pathogen, ranging from being protective from infection to promoting pathology. More studies are needed in order to understand the basic immunological mechanisms leading to

autoimmune- like responses during infection and their possible contribution to pathology and/or protection from infection. Mechanistic studies to understand the role of autoimmune antibodies should be performed to elucidate the role of these antibodies in pathogen infectivity – do autoimmune antibodies neutralize pathogens and/or recognize infected cells and target them for clearance or complement lysis?. Similarly, the role of autoimmune antibodies in disease pathology – do these antibodies mediate pathological processes that take place during or after infection? – should be studied *in vitro* and in animal models of infection (see Outstanding Questions). Epidemiological studies in human patients will also be essential to assess the relevance of these autoantibodies as inductors of pathogenesis and/or as controllers of infection.

References

- Berlin T, et al. 2007; Autoantibodies in nonautoimmune individuals during infections. *Annals of the New York Academy of Sciences*. 1108:584–93. [PubMed: 17894023]
- Ercolini AM, Miller SD. 2009; The role of infections in autoimmune disease. *Clinical and experimental immunology*. 155(1):1–15. [PubMed: 19076824]
- Arroyo-Avila M, et al. 2017; Clinical Manifestations Associated with Peripheral Joint Involvement in Patients with Acute Chikungunya Virus Infection. *The American journal of tropical medicine and hygiene*. 96(4):916–921. [PubMed: 28138049]
- Fernandez-Arias C, et al. 2016; Anti-Self Phosphatidylserine Antibodies Recognize Uninfected Erythrocytes Promoting Malarial Anemia. *Cell host & microbe*. 19(2):194–203. [PubMed: 26867178]
- Draborg A, et al. 2016; How compelling are the data for Epstein-Barr virus being a trigger for systemic lupus and other autoimmune diseases? *Current opinion in rheumatology*. 28(4):398–404. [PubMed: 26986247]
- Goodfellow JA, Willison HJ. 2016; Guillain-Barre syndrome: a century of progress. *Nature reviews. Neurology*. 12(12):723–731. [PubMed: 27857121]
- Godschalk PC, et al. 2007; Structural characterization of *Campylobacter jejuni* lipooligosaccharide outer cores associated with Guillain-Barre and Miller Fisher syndromes. *Infection and immunity*. 75(3):1245–54. [PubMed: 17261613]
- Shoenfeld Y, et al. 1986; Monoclonal anti-tuberculosis antibodies react with DNA, and monoclonal anti-DNA autoantibodies react with *Mycobacterium tuberculosis*. *Clinical and experimental immunology*. 66(2):255–61. [PubMed: 3102132]
- Elkington P, et al. 2016; Tuberculosis: An Infection-Initiated Autoimmune Disease? *Trends in immunology*. 37(12):815–818. [PubMed: 27773684]
- Barnett LA, Cunningham MW. 1992; Evidence for actinlike proteins in an M protein-negative strain of *Streptococcus pyogenes*. *Infection and immunity*. 60(9):3932–6. [PubMed: 1386840]
- Ringrose JH, et al. 2001; Influence of infection of cells with bacteria associated with reactive arthritis on the peptide repertoire presented by HLA-B27. *Journal of medical microbiology*. 50(4):385–9. [PubMed: 11289525]
- Clark SE, Weiser JN. 2013; Microbial modulation of host immunity with the small molecule phosphorylcholine. *Infection and immunity*. 81(2):392–401. [PubMed: 23230294]
- Yilmaz B, et al. 2014; Gut microbiota elicits a protective immune response against malaria transmission. *Cell*. 159(6):1277–89. [PubMed: 25480293]
- Flodstrom-Tullberg M. 2003; Viral infections: their elusive role in regulating susceptibility to autoimmune disease. *Microbes and infection*. 5(10):911–21. [PubMed: 12919859]
- Monsalve DM, et al. 2017 Zika virus and autoimmunity. *One-step forward. Autoimmunity reviews*.
- Sene D, et al. 2008; Antiphospholipid antibodies, antiphospholipid syndrome and infections. *Autoimmunity reviews*. 7(4):272–7. [PubMed: 18295729]

17. Tanay A. 2017; Chikungunya virus and autoimmunity. *Current opinion in rheumatology*. 29(4): 389–393. [PubMed: 28376065]
18. Wan SW, et al. 2013; Autoimmunity in dengue pathogenesis. *Journal of the Formosan Medical Association = Taiwan yi zhi*. 112(1):3–11. [PubMed: 23332423]
19. Garzelli C, et al. 1989; Mechanisms other than polyclonal B cell activation possibly involved in Epstein-Barr virus-induced autoimmunity. *Clinical and experimental immunology*. 76(3):412–6. [PubMed: 2546702]
20. Kivity S, et al. 2009; Infections and autoimmunity—friends or foes? *Trends in immunology*. 30(8): 409–14. [PubMed: 19643667]
21. Stratton R, et al. 2009; Autoimmunity and HIV. *Current opinion in infectious diseases*. 22(1):49–56. [PubMed: 19532080]
22. Matsuda J, et al. 1995; High prevalence of anti-phospholipid antibodies and anti-thyroglobulin antibody in patients with hepatitis C virus infection treated with interferon-alpha. *The American journal of gastroenterology*. 90(7):1138–41. [PubMed: 7611213]
23. Rubtsova K, et al. 2013; T-box transcription factor T-bet, a key player in a unique type of B- cell activation essential for effective viral clearance. *Proc Natl Acad Sci U S A*. 110(34):E3216–24. [PubMed: 23922396]
24. Yee LJ, et al. 2004; Antinuclear antibodies (ANA) in chronic hepatitis C virus infection: correlates of positivity and clinical relevance. *Journal of viral hepatitis*. 11(5):459–64. [PubMed: 15357653]
25. Gabriel E, et al. 2017; Recent Zika Virus Isolates Induce Premature Differentiation of Neural Progenitors in Human Brain Organoids. *Cell stem cell*. 20(3):397–406 e5. [PubMed: 28132835]
26. Li C, et al. 2016; Zika Virus Disrupts Neural Progenitor Development and Leads to Microcephaly in Mice. *Cell stem cell*. 19(5):672. [PubMed: 27814481]
27. Tang H, et al. 2016; Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth. *Cell stem cell*. 18(5):587–90. [PubMed: 26952870]
28. Anaya JM, et al. 2016; Zika virus and neurologic autoimmunity: the putative role of gangliosides. *BMC medicine*. 14:49. [PubMed: 27001187]
29. Pinto-Diaz CA, et al. 2017; Autoimmunity in Guillain-Barre syndrome associated with Zika virus infection and beyond. *Autoimmunity reviews*. 16(4):327–334. [PubMed: 28216074]
30. Tsunoda I, et al. 2016; Neuropathogenesis of Zika Virus Infection : Potential Roles of Antibody-Mediated Pathology. *Acta medica Kinki University*. 41(2):37–52. [PubMed: 28428682]
31. Nico D, et al. 2018; Prevalence of IgG autoantibodies against GD3 ganglioside in acute Zika virus infection. *Frontiers in Medicine*. 5(25)
32. Manimunda SP, et al. 2010; Clinical progression of chikungunya fever during acute and chronic arthritic stages and the changes in joint morphology as revealed by imaging. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 104(6):392–9. [PubMed: 20171708]
33. Agrawal S, et al. 2007; Autoantibodies in rheumatoid arthritis: association with severity of disease in established RA. *Clinical rheumatology*. 26(2):201–4. [PubMed: 16572283]
34. Song YW, Kang EH. 2010; Autoantibodies in rheumatoid arthritis: rheumatoid factors and anticitrullinated protein antibodies. *QJM: monthly journal of the Association of Physicians*. 103(3):139–46. [PubMed: 19926660]
35. Leadbetter EA, et al. 2002; Chromatin-IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. *Nature*. 416(6881):603–7. [PubMed: 11948342]
36. Marshak-Rothstein A. 2006; Toll-like receptors in systemic autoimmune disease. *Nature reviews. Immunology*. 6(11):823–35. [PubMed: 17063184]
37. Hao Y, et al. 2011; A B-cell subset uniquely responsive to innate stimuli accumulates in aged mice. *Blood*. 118(5):1294–304. [PubMed: 21562046]
38. Daniel-Ribeiro CT, Zanini G. 2000; Autoimmunity and malaria: what are they doing together? *Acta tropica*. 76(3):205–21. [PubMed: 10974161]
39. Miloudi M, et al. 2017; Immune thrombocytopenia associated with malaria: a case report. *Annales de biologie clinique*. 75(5):569–571. [PubMed: 28958967]

40. Mourao LC, et al. 2016; Anti-erythrocyte antibodies may contribute to anaemia in *Plasmodium vivax* malaria by decreasing red blood cell deformability and increasing erythrophagocytosis. *Malar J.* 15(1):397. [PubMed: 27488382]
41. Zaccane P, et al. 2008; Interplay of parasite-driven immune responses and autoimmunity. *Trends in parasitology.* 24(1):35–42. [PubMed: 18055264]
42. Cunha-Neto E, et al. 1995; Autoimmunity in Chagas disease cardiopathy: biological relevance of a cardiac myosin-specific epitope crossreactive to an immunodominant *Trypanosoma cruzi* antigen. *Proceedings of the National Academy of Sciences of the United States of America.* 92(8):3541–5. [PubMed: 7536937]
43. 2017Malaria vaccine: WHO position paper, January 2016- Recommendations. Vaccine.
44. Rosenberg YJ. 1978; Autoimmune and polyclonal B cell responses during murine malaria. *Nature.* 274(5667):170–2. [PubMed: 351426]
45. Rivera-Correa, J, R, A. A Role for Autoimmunity in the Immune Response against Malaria. In: Rodriguez, A, Mota, M, editors *Malaria - Immune Response to Infection and Vaccination.* Springer; 2016.
46. Rivera-Correa J, et al. 2017; *Plasmodium* DNA-mediated TLR9 activation of T-bet(+) B cells contributes to autoimmune anaemia during malaria. *Nature communications.* 8(1):1282.
47. Mannoor K, et al. 2013; Induction of ssDNA-binding autoantibody secreting B cell immunity during murine malaria infection is a critical part of the protective immune responses. *Immunobiology.* 218(1):10–20. [PubMed: 22361243]
48. Wozencraft AO, et al. 1990; Role of DNA-binding antibodies in kidney pathology associated with murine malaria infections. *Infection and immunity.* 58(7):2156–64. [PubMed: 2365456]
49. Viotti R, et al. 2014; Towards a paradigm shift in the treatment of chronic Chagas disease. *Antimicrobial agents and chemotherapy.* 58(2):635–9. [PubMed: 24247135]
50. Radon K, et al. 2003; *Toxoplasma gondii* infection, atopy and autoimmune disease. *European journal of medical research.* 8(4):147–53. [PubMed: 12765860]
51. Rubtsova K, et al. 2017; B cells expressing the transcription factor T-bet drive lupus-like autoimmunity. *The Journal of clinical investigation.* 127(4):1392–1404. [PubMed: 28240602]
52. Litwin CM, Binder SM. 2016; ANA testing in the presence of acute and chronic infections. *J Immunoassay Immunochem.* 37(5):439–52. [PubMed: 27050929]
53. Faaber P, et al. 1984; Cross-reactivity of anti-DNA antibodies with proteoglycans. *Clinical and experimental immunology.* 55(3):502–8. [PubMed: 6608423]
54. Elkon KB, Silverman GJ. 2012; Naturally occurring autoantibodies to apoptotic cells. *Advances in experimental medicine and biology.* 750:14–26. [PubMed: 22903663]
55. Venuti A, et al. 2017; The Role of Natural Antibodies to CC Chemokine Receptor 5 in HIV Infection. *Frontiers in immunology.* 8:1358. [PubMed: 29163468]
56. Baumgarth N. 2011; The double life of a B-1 cell: self-reactivity selects for protective effector functions. *Nat Rev Immunol.* 11(1):34–46. [PubMed: 21151033]
57. Shaw PX, et al. 2000; Natural antibodies with the T15 idiotype may act in atherosclerosis, apoptotic clearance, and protective immunity. *J Clin Invest.* 105(12):1731–40. [PubMed: 10862788]
58. Gronwall C, Silverman GJ. 2014; Natural IgM: beneficial autoantibodies for the control of inflammatory and autoimmune disease. *J Clin Immunol* 34 Suppl. 1:S12–21.
59. Schwartz-Albiez R, et al. 2009; Natural antibodies, intravenous immunoglobulin and their role in autoimmunity, cancer and inflammation. *Clin Exp Immunol.* 158(Suppl 1):43–50. [PubMed: 19883423]
60. Lobo PI. 2017; Role of Natural IgM Autoantibodies (IgM-NAA) and IgM Anti-Leukocyte Antibodies (IgM-ALA) in Regulating Inflammation. *Current topics in microbiology and immunology.* 408:89–117. [PubMed: 28698955]
61. Abdel-Wahab N, et al. 2017Risk of developing antiphospholipid antibodies following viral infection: a systematic review and meta-analysis. *Lupus.*
62. Callahan MK, et al. 2003; Phosphatidylserine on HIV envelope is a cofactor for infection of monocytic cells. *J Immunol.* 170(9):4840–5. [PubMed: 12707367]

63. Martin-Acebes MA, et al. 2016; Lipids and flaviviruses, present and future perspectives for the control of dengue, Zika, and West Nile viruses. *Progress in lipid research*. 64:123–137. [PubMed: 27702593]
64. Mercer J, Helenius A. 2010; Apoptotic mimicry: phosphatidylserine-mediated macropinocytosis of vaccinia virus. *Ann N Y Acad Sci*. 1209:49–55. [PubMed: 20958316]
65. Dowall SD, et al. 2015; Effective binding of a phosphatidylserine-targeting antibody to Ebola virus infected cells and purified virions. *J Immunol Res*. 2015:347903. [PubMed: 25815346]
66. Soares MM, et al. 2008; Targeting inside-out phosphatidylserine as a therapeutic strategy for viral diseases. *Nat Med*. 14(12):1357–62. [PubMed: 19029986]

Outstanding Questions

- Do infection-induced anti-self antibodies inhibit microbial ability to infect host cells? Anti- self antibodies may be important in microbe clearance, since they may recognize antigens in the surface and target the pathogen for opsonization. They may even neutralize the microbe by direct binding to molecules required for host-cell invasion.
- Are infected cells recognized by anti-self antibodies and targeted for early clearance? Infected cells may be exposing self antigens in their surface, such as PS, that could be recognized by anti-self antibodies, targeting cells for clearance by the immune system.
- What are the mechanisms underlying anti-self antibody generation during infection and maintenance after recovery? Some recent knowledge suggests that inflammation together with pathogen induced TLR activation and antigen presentation induces the generation of anti-self antibodies. However, the regulation of these mechanisms and the establishment of immune memory in anti-self antibodies remain unknown.

Highlights

- Anti-self antibodies are frequently generated during several viral, bacterial or parasitic infections.
- Infection-induced anti-self antibodies may lead to transient autoimmune pathology or persistent autoimmune disorders after infection is cleared.
- Anti-self antibodies may also contribute to protection from infection by interfering with host-cell invasion and/or by facilitating the detection and elimination of infected cells.
- Given their potential contribution to pathogen clearance, the generation of infection- induced anti-self antibodies may be part of a normal response, and not merely an erroneous immune reaction.

Fig 1. Anti-self antibodies generated during infection can contribute to induce pathology and/or protection

Infection by virus, bacteria or parasites frequently induces anti-self antibodies. These antibodies recognize self antigens and occasionally induce pathologies similar to classical autoimmune diseases. Anti-self antibodies may also be able to bind directly to pathogens and/or infected cells, contributing to protection against infection