Published in final edited form as:
Immunol Cell Biol. 2010 August ; 88(6): 614–615. doi:10.1038/icb.2010.72.

Anti-cytokine autoantibodies explain some chronic mucocutaneous candidiasis

Sarah K Browne and **Steven M Holland**
Laboratory of Clincial Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, CRC B3-4141, MSC 1684, Bethesda, MD 20892-1684, USA

Steven M Holland: smh@nih.gov

'Know thyself'

From the Temple of Apollo at Delphi.

Anti-cytokine autoantibodies are increasing their visibility as important mechanisms of disease pathogenesis. Pulmonary alveolar proteinosis (PAP) can be caused by anti- GM-CSF autoantibodies,[1] pure red-cell apla- sia can be caused by anti-erythropoietin autoantibodies,[2,3] disseminated non-tuber- culous mycobacterial infections can be caused by anti-interferon (IFN)-gamma autoantibodies[4–7] and staphylococcal infections have been associated with anti-IL-6 autoantibodies.[8] Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED) syndrome is caused by mutations in the autoimmune regulator (AIRE),[9] leading to loss of thymic deletion of autoreactive T cells with multiple autoimmune consequences such as hypoparathyroidism, diabetes, and adrenal failure.[10] Interestingly, anti-cytokine autoantibodies are extremely common in APECED, mostly directed against type I IFNs.[11] However, one of the puzzling components of APECED is severe chronic mucocutaneous candidiasis (CMC). APECED patients are not susceptible to other overt infections, and even CMC remains blocked in the mucosa. In the February 15, 2010 issue of the *Journal of Experimental Medicine*, Puel *et al*.[12] and Kisand *et al*.[13] have offered elegant explanations of why CMC occurs in APECED: high-titer, neutralizing autoantibodies to the T-cell cytokines that regulate mucosal antibacterial and anti-fungal activity, IL-17 and IL-22. These cytokines were good targets for involvement in CMC: STAT3-deficient hyper IgE (Job's) syndrome,[14,15] dectin-1 deficiency,[16] CARD9 deficiency,[17] and to a lesser extent, IL-12 receptor b1 deficiency,[14] all have CMC and varying degrees of Th17 impairment, linking this pathway to mucosal candidiasis.

Puel *et al*. examined 33 APECED patients and identified antibodies to IL-17A, IL-17F, and IL-22 in all the 33 APECED patients tested, 29 of whom also had CMC; healthy controls had neither those autoantibodies nor CMC.[12] They confirmed the function of the anti-IL-17A antibody by inhibiting IL-6 production from IL-17 responsive fibroblasts.[18]

Kisand *et al*. examined 162 APECED patients and found anti-IL-17 A, IL-17F, and IL-22 autoantibodies in up to 90% of cases, strongly associated with CMC.[13] Titers of

CONFLICT OF INTEREST
The authors declare no conflict of interest.

autoantibodies to IL-17 and IL-22 actually declined with age in APECED, whereas titers of autoantibodies against type 1 IFNs, did not. Exploring specificity, Kisand *et al*. noted that homozygous cases of the common AIRE mutation R257X were always associated with anti-IL-17 and anti-IL-2 autoantibodies and CMC, whereas other mutations were more variable. They did not find autoantibodies to IL-17 or IL-22 in cases of CMC without other features of APECED or AIRE mutation, but they did find these autoantibodies in two out of 35 patients with thymoma and CMC.[13] Therefore, CMC with immune dysregulation is often associated with anti-cytokine autoantibodies. Kisand *et al*. and Puel *et al*. found only IgG autoantibodies in this syndrome limited to the mucosa, but not in secreted IgA.

What are we to make of these exciting observations? Although anti-cytokine autoantibodies leading to immunodeficiency have been described earlier, they have been in the setting of rare infections and are still unassociated with specific mutations. Autoantibodies provide novel facets to PAP, non-tuberculous mycobacteria, and staphylococcal infections, but we are still woefully ignorant about why the antibodies happen or what really to do about them. In contrast, Kisand *et al*. and Puel *et al.* describe pathogenic autoantibodies in the context of a disease with recognized mutations that was recognized earlier. Kisand *et al*. even point out the genotype–phenotype associations with a specific mutation in AIRE. This is a first pass at identifying fundamental mechanisms around the generation of autoantibodies in general, and specific ones in particular.

Now that it is clear that certain anti-cytokine autoantibodies result in opportunistic infections, we need to address the mechanisms of pathogenicity of these autoantibodies. Functional demonstration of neutralization of cognate cytokines by certain autoantibodies is complemented by the knowledge of genetic defects in the cytokine pathways leading to similar infections. For instance, defects in the IFNg/IL-12 signalling pathways (*IFNGR1*, *IFNGR2*, *STAT1*, *IL-12B [p40]*, *IL-12RB1*, *IKBKG/NEMO*) lead to disseminated mycobacterial infection.[19] Mutations in the STAT3/IL-6 signalling pathways (*STAT3*, *TYK2*)[6,20] lead to severe staphylococcal skin infections. In contrast, the genetically defined pathways leading to CMC, other than those seen with profound T-lymphocyte dysfunction, include STAT3, DOCK8, Tyk2, IL-12Rb1, as well as dectin-1, CARD9, and AIRE. Uniting many of these pathways are defects in IL-17 and IL-22 generation and response, giving further weight to the observations of IL-17 and IL-22 blockade in AIRE deficiency.

As both Puel *et al*. and Kisand *et al*. report a few instances of autoantibodies without CMC, and there are many instances of CMC outside of APECED without autoantibodies, autoantibodies to IL-17 and IL-22 are likely not the complete story. Single anti-cytokine autoantibodies may be necessary and sufficient for some diseases (for example, anti-GM-CSF autoantibodies in PAP), but others may require combinations of factors or perhaps multiple autoantibodies acting in concert.

The potential exists for an indefinite number of autoantibodies to be involved on both sides of disease causation. Autoantibodies to antimicrobial peptides, hormones and/or cell surface receptors are likely to be involved in the disease. In addition, it is possible that autoantibodies could actually facilitate or exacerbate inflammation by inhibiting anti-inflammatory cytokines, such as IL-10. Therefore, broad searches for etiologies of new and

old syndromes will have to incorporate an increasingly dizzying array of etiologic possibilities.

The association of specific diseases with only a particular set of anti-cytokine autoantibodies is a remarkable feature of these entities. Although thymoma and APECED share high rates of anti-IFNa autoantibodies, only thymoma shows IL-12 autoantibodies,[21] but neither disease has anti-IFNg or anti-GM-CSF autoantibodies. Despite the challenges of identifying and characterizing anti-cytokine autoantibodies in the disease, they open exciting new possibilities for treatment. Plasmapheresis and intravenous immune globulin have been tried in many autoantibody-mediated diseases, but their results are typically modest. The CD20+ B-cell-targeted therapeutic antibody, rituximab, has been used in small series in a variety of diseases mediated by autoantibodies with encouraging results.[22–24]

Autoantibodies to cytokines represent an emerging layer of immune regulation. Unlike primary congenital immunodeficiencies, these may develop over time, wax and wane, and change in titer or avidity. Antibodies targeting a given cytokine can be found incidentally in healthy hosts and associated with disease ranging from mild to severe. Whether involved in normal cytokine homeostasis or pathology, anti-cytokine autoantibodies have the proven potential to modulate cytokine pathways. The new work highlighting the functions of autoantibodies to IL-17 and IL-22 in CMC in APECED is a strong start in an exciting direction.

References

1. Kitamura T, Tanaka N, Watanabe J, Uchida, Kanegasaki S, Yamada Y, et al. Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. J Exp Med. 1999; 190:875–880. [PubMed: 10499925]
2. Casadevall N, Dupuy E, Molho-Sabatier P, Tobelem G, Varet B, Mayeux P. Autoantibodies against erythropoietin in a patient with pure red-cell aplasia. N Engl J Med. 1996; 334:630–633. [PubMed: 8592526]
3. Casadevall N, Nataf J, Viron B, Kolta A, Kiladjian JJ, Martin-Dupont P, et al. Pure red-cell aplasia and anti-erythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med. 2002; 346:469–475. [PubMed: 11844847]
4. Doffinger R, Helbert MR, Barcenas-Morales G, Yang K, Dupuis S, Ceron-Gutierrez L, et al. Autoantibodies to interferon-gamma in a patient with selective susceptibility to mycobacterial infection and organ-specific autoimmunity. Clin Infect Dis. 2004; 38:e10–e14. [PubMed: 14679469]
5. Hoflich C, Sabat R, Rosseau S, Temmesfeld B, Slevogt H, Docke WD, et al. Naturally occurring anti-IFN-gamma autoantibody and severe infections with Mycobacterium cheloneae and Burkholderia cocovenenans. Blood. 2004; 103:673–675. [PubMed: 12947000]
6. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. N Engl J Med. 2007; 357:1608–1619. [PubMed: 17881745]
7. Kampmann B, Hemingway C, Stephens A, Davidson R, Goodsall A, Anderson S, et al. Acquired predisposition to mycobacterial disease due to autoantibodies to IFN-gamma. J Clin Invest. 2005; 115:2480–2488. [PubMed: 16127458]
8. Puel A, Picard C, Lorrot M, Pons C, Chrabieh M, Lorenzo L, et al. Recurrent staphylococcal cellulitis and subcutaneous abscesses in a child with autoantibodies against IL-6. J Immunol. 2008; 180:647–654. [PubMed: 18097067]
9. Finnish-German APECED Consortium. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. Nat Genet. 1997; 17:399–403. [PubMed: 9398840]

10. Anderson MS, Venanzi ES, Klein L, Chen Z, Berzins SP, Turley SJ, et al. Projection of an immunological self shadow within the thymus by the aire protein. Science. 2002; 298:1395–1401. [PubMed: 12376594]
11. Meager A, Visvalingam K, Peterson P, Moll K, Murumagi A, Krohn K, et al. Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. PLoS Med. 2006; 3:e289. [PubMed: 16784312]
12. Puel A, Doffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. J Exp Med. 2010; 207:291–297. [PubMed: 20123958]
13. Kisand K, Boe Wolff AS, Podkrajsek KT, Tserel L, Link M, Kisand KV, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. J Exp Med. 2010; 207:299–308. [PubMed: 20123959]
14. de Beaucoudrey L, Puel A, Filipe-Santos O, Cobat A, Ghandil P, Chrabieh M, et al. Mutations in STAT3 and IL12RB1 impair the development of human IL-17-producing T cells. J Exp Med. 2008; 205:1543–1550. [PubMed: 18591412]
15. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature. 2008; 452:773–776. [PubMed: 18337720]
16. Ferwerda B, Ferwerda G, Plantinga TS, Willment JA, van Spriel AB, Venselaar H, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med. 2009; 361:1760–1767. [PubMed: 19864674]
17. Glocker EO, Hennigs A, Nabavi M, Schaffer AA, Woellner C, Salzer U, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Engl J Med. 2009; 361:1727–1735. [PubMed: 19864672]
18. Yao Z, Spriggs MK, Derry JM, Strockbine L, Park LS, VandenBos T, et al. Molecular characterization of the human interleukin (IL)-17 receptor. Cytokine. 1997; 9:794–800. [PubMed: 9367539]
19. Reichenbach J, Rosenzweig S, Doffinger R, Dupuis S, Holland SM, Casanova JL. Mycobacterial diseases in primary immunodeficiencies. Curr Opin Allergy Clin Immunol. 2001; 1:503–511. [PubMed: 11964733]
20. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. Nature. 2007; 448:1058–1062. [PubMed: 17676033]
21. Meager A, Vincent A, Newsom-Davis J, Willcox N. Spontaneous neutralising antibodies to interferon–alpha and interleukin-12 in thymoma-associated autoimmune disease. Lancet. 1997; 350:1596–1597. [PubMed: 9393342]
22. Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. N Engl J Med. 2006; 355:1772–1779. [PubMed: 17065638]
23. Borie R, Debray MP, Laine C, Aubier M, Crestani B. Rituximab therapy in autoimmune pulmonary alveolar proteinosis. Eur Respir J. 2009; 33:1503–1506. [PubMed: 19483052]
24. Illa I, Diaz-Manera J, Rojas-Garcia R, Pradas J, Rey A, Blesa R, et al. Sustained response to Rituximab in anti-AChR and anti-MuSK positive Myasthenia Gravis patients. J Neuroimmunol. 2008; 201–202:90–94.