

Review Article

Infectious diseases and autoimmunity

Lucia G. Delogu¹, Silvia Deidda², Giuseppe Delitala², Roberto Manetti²

¹Department of Drug Science, University of Sassari, Italy

²Department of Clinical, Experimental and Oncological Medicine, University of Sassari, Italy

Abstract

Introduction: Autoimmunity occurs when the immune system recognizes and attacks host tissue. In addition to genetic factors, environmental triggers (in particular viruses, bacteria and other infectious pathogens) are thought to play a major role in the development of autoimmune diseases.

Methodology: We searched PubMed, Cochrane, and Scopus without time limits for relevant articles.

Results: In this review, we (i) describe the ways in which an infectious agent can initiate or exacerbate autoimmunity; (ii) discuss the evidence linking certain infectious agents to autoimmune diseases in humans; and (iii) describe the animal models used to study the link between infection and autoimmunity.

Conclusions: Besides genetic predisposition to autoimmunity, viral and bacterial infections are known to be involved in the initiation and promotion of autoimmune diseases. These studies suggest that pathogens can trigger autoimmunity through molecular mimicry and their adjuvant effects during initiation of disease, and can promote autoimmune responses through bystander activation or epitope spreading via inflammation and/or superantigens.

Key words: viral infection; bacterial infection; autoreactive lymphocyte; molecular mimicry; bystander activation; epitope spreading; autoimmune disease

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Introduction

The immune system must distinguish self from harmful non-self to repel invaders and to preserve the integrity of the host without inducing autoimmunity. Any deficit in this function can result in susceptibility to infections, malignancies [1-3] or over-reactivity to harmless antigens, leading to immunopathology and autoimmunity. The etiology of autoimmune diseases has been difficult to elucidate. Several factors are thought to contribute to the development of immune response to self, including genetics and environment [4-6]

Several common autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis, are genetically linked to distinct human major histocompatibility complex (MHC) class II molecules and other immune modulators. Furthermore, autoimmunity often clusters families, indicating the potential for a broad-spectrum genetic defect in immunological tolerance mechanisms. However, the genetic factors leading to the development of immune responses against specific antigens in a tissue and/or organ-specific manner

remain largely unknown. Among the environmental factors, infections have been implicated in the onset and/or promotion of autoimmunity [7].

This article reviews the evidence regarding the association of pathogens with autoimmune diseases. We searched PubMed, Cochrane, and Scopus without time limits. The following search terms were employed in various combinations: “bacterium”, “parasite”, “virus”, “infection” and “autoimmunity”.

There are more than eighty identified autoimmune diseases [8]. Multiple arms of the immune system may be involved in autoimmune pathology. Antigens are taken up by antigen presenting cells (APC) such as dendritic cells (DC) and processed into peptides which are loaded onto MHC molecules for presentation to T cells via clonotypic T cell receptors (TCR). Cytolytic T cells (T_c, activated by MHC class I on APC) can directly lyse a target, while T helper cells (T_h, activated by MHC class II) release cytokines that can have direct effects or can activate macrophages, monocytes and B cells. B cells themselves have surface receptors that can bind surface antigens. Upon receiving signals from T_h cells, B cells secrete

antibodies specific for the antigens. Antibody may bind its specific target alone or may bind to and activate macrophages simultaneously via the Fc receptor.

Multiple mechanisms have been described to explain how pathogens might induce activation and critical expansion of autoreactive T cells and start autoimmune disease [9-14]. A microbial antigen can include an epitope that is structurally similar to an autoantigen epitope, providing the basic element of the mechanism referred to as molecular mimicry [13-18]. Another mechanism would imply that the inflammatory setting and the paracrine secretion of T cell growth factors induce the expansion of activated autoreactive T cells, whose small number was previously insufficient to drive an autoimmune disease. Such a mechanism is referred to as bystander activation [19]. Pathogen-induced tissue inflammation may result in local activation of APC and enhanced processing/presentation of self-antigens that causes T cell priming, followed by T cell activation and expansion of additional specificities (epitope spreading) [20,21]. Activation of resting autoreactive T cells may be achieved by viral and bacterial superantigens that bind a variety of MHC class II molecules and activate large numbers of T cells, irrespective of their specificity [22].

In this review, we outline the mechanisms by which pathogens could trigger autoimmune diseases and the evidence available for the involvement of specific pathogens in the initiation or exacerbation of representative autoimmune diseases.

Pathogen responses and autoimmunity

The ability of the host to defend against invading pathogens is to a large extent mediated by a group of germline-encoded receptors known as pattern-recognition receptors (PRR). These molecules include Toll-like receptors (TLR), nucleotide-binding and oligomerization domain (NOD)-like receptors (NLR), (RIG-I)-like helicases and a subset of C-type lectin receptors, which together recognize a large number of molecular patterns present in bacteria, viruses and fungi [23]. The signalling pathways that are triggered by engagement of these molecules lead to cellular activation, which increases the antigen-presenting capacity of and the expression of co-stimulatory molecules by APC, as well as their production of type I interferons, pro-inflammatory cytokines and chemokines, which initiate and direct the immune response against the invading pathogen. Microbial antigens as well as PRR-triggered inflammatory

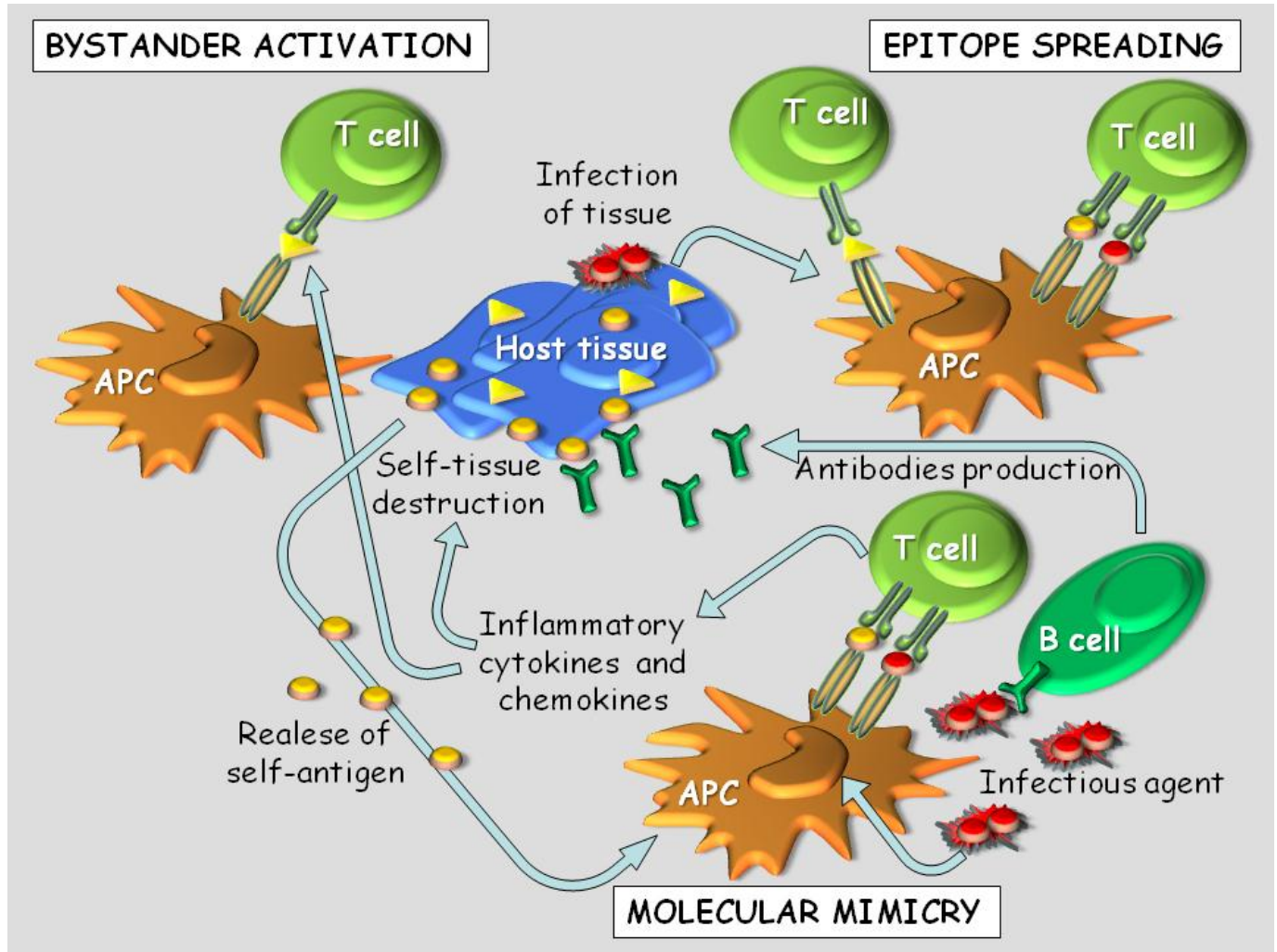
molecules drive the clonal expansion of pathogen-specific T and B cells. By triggering PRRs, stimulating early responses by the innate immune system and increasing the function of APC, pathogens act as adjuvants for the immune response, while at the same time providing an antigen source to drive T-cell and B-cell activation. In this highly inflammatory environment, it is easy to envision how an aberrant destructive immune response can be triggered and/or escalated if autoreactive cells are present. There are several postulated mechanisms by which pathogenic infections can trigger autoimmune disease (Figure 1).

Molecular mimicry

Antigen recognition by the TCR allows T-cell activation by different peptides bound to one or even several MHC molecules [24]. The pathogen may carry elements that are similar enough in amino acid sequence or structure to self-antigen, so T cells that are activated in response to the pathogen are also cross-reactive to self and lead to direct damage and further activation of other arms of the immune system. Similarly, antibodies reflecting B-cell receptor specificity were found to recognize both microbial and self-antigens [25]. This hypothesis is known as molecular mimicry [10,26]. It is now generally accepted that a single T cell can respond to various distinct peptides, and that different peptide/MHC complexes can lead to cross-reactivity by the same TCR as long as the complexes have similar charge distribution and overall shape [27-29]. This flexibility of TCR recognition is thought to be central to many immunological processes including thymic selection and the ability to recognize nearly all pathogen-derived peptides. A side effect of this is the induction of autoimmunity by microbial antigens [7].

Animal models in which molecular mimicry can trigger autoimmune disease are abundant. These include: Theiler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease (TMEV-IDD), a model of human multiple sclerosis in which intracerebral TMEV infection of mice leads to an autoimmune demyelinating disorder 30-40 days after infection [21]; herpes simplex virus (HSV)-associated stromal keratitis, in which HSV infection leads to blindness secondary to corneal-antigen-specific T-cell responses in both humans and mice [30-33]; cytotoxic reactions caused by antibodies against *Streptococcus pyogenes* antigens, which may be one mechanism to explain the origin of autoimmune heart disease in rheumatoid myocarditis [34]; infection of prediabetic mice with a virus expressing an H-2Kb-restricted

Figure 1. Mechanism by which pathogens may cause autoimmunity. a) Molecular mimicry describes the activation of crossreactive T cells that recognize both the pathogen-derived epitopes and the self-derived epitopes. Pathogen-derived epitopes are taken up by APC and presented to T cells. Activation of T cells results in the direct lysis of self-tissue or release of cytokines and chemokines that activate macrophages, which mediate self-tissue damage, and provide help to pathogen-specific B cells. The subsequent release of self-tissue antigens and their uptake by APC perpetuates the autoimmune disease. b) Bystander activation is the nonspecific activation of self-reactive T cells. Activation of pathogen-specific T cells leads to inflammation that damages self-tissue in an antigen non-specific manner, and triggers activation of self-reactive T cells. c) Epitope spreading involves a persistent pathogen infection that causes damage to self-tissue. This results in the release of self-peptides, which are engulfed by APC and presented to self-reactive T cells. Continual damage and release of self-peptides results in the spread of the self-reactive immune response to multiple self-epitopes.



mimic ligand to a self-epitope present on beta cells, which accelerates the development of autoimmune diabetes [35]; autoimmune demyelinating disease associated with Semliki Forest virus (SFV) [36]; autoimmune myocarditis associated with coxsackie virus infection [37]; and murine cytomegalovirus [38]. T cells with low affinity for a self-antigen and that have escaped thymus negative selection, as would be the case for many self-antigen-specific responses, can become activated by infection with a microorganism containing an identical antigen, which provides appropriate innate immune signals, resulting in overt autoimmune disease.

In keeping with the observation that specific T cells that have been primed by pathogens and cross-react with self-antigens can cause autoimmunity in animal models, patients with autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis have been found to have higher frequencies activated self-reactive lymphocytes [39-42]. In multiple sclerosis, receptor analysis of T and B cells in central nervous system (CNS) tissue and in the cerebrospinal fluid (CSF) showed clonal expansions in both populations, indicating that there is clonal reactivity to a restricted number of disease-relevant antigens [43-45]. In

addition, longitudinal studies provided evidence for long-term persistence of individual myelin-specific T-cell clones tracked over several years in the blood of patients with multiple sclerosis [46-48], indicating a strong, persisting memory response and/or ongoing autoantigen exposure at least for a subset of myelin-reactive T cells in multiple sclerosis. These memory responses may reflect, at least in part, persisting clonal expansions of polyspecific T cells recognizing both self and virus antigens. For example, high viral loads that occur during symptomatic primary EBV infection, resulting in infectious mononucleosis, are associated with an increased risk of developing multiple sclerosis [49-51], and could prime these polyspecific T-cell responses. Accordingly, patients with multiple sclerosis have predominant clonal expansions of T cells specific for the EBV-encoded nuclear antigen 1 (EBNA1), which is the most consistently recognized EBV-derived CD4+ T-cell antigen in healthy virus carriers, and EBNA1-specific T cells recognize myelin antigens more frequently than other autoantigens that are not associated with multiple sclerosis [52].

Autoimmune chronic gastritis (AIG) is an organ-specific inflammatory disease, characterized by lymphocytic infiltrates in the gastric mucosa and by destruction of parietal cells, resulting in mucosal atrophy, hypochloridria, and eventually pernicious anemia. [53]. In most AIG patients, serum anti-parietal cell autoantibodies (PCAs) are detectable. The autoantigen recognized is the gastric H+K+ adenosine triphosphatase (ATPase), the proton pump, localized in the parietal cell canaliculi [54,55]. H+K+ ATPase is also the target of autoreactive T cells that infiltrate the gastric mucosa of AIG patients [56]. Autoimmune gastritis and *Helicobacter pylori*-associated gastric atrophy develop through similar mechanisms involving the proton pump H+K+ ATPase as autoantigen. *Helicobacter pylori*-infected patients with gastric autoimmunity harbor in vivo activated gastric Th1 CD4 cells that recognize both H+K+ ATPase and *Helicobacter pylori* antigens [57,58]. So, in genetically susceptible individuals, *Helicobacter pylori* infection can activate cross-reactive gastric T cells leading to gastric autoimmunity via molecular mimicry.

Bystander activation of autoreactive cells and epitope spreading

Bystander activation describes an indirect or non-specific activation of autoimmune cells caused by the inflammatory environment present during infection. APCs that have become activated within the inflammatory milieu of a pathogenic infection can

stimulate the activation and proliferation of autoreactive T or B cells. In this case, APC present self-antigen, obtained subsequent to tissue destruction and/or the uptake of local dying cells, to autoreactive cells [59,60]. In addition to autoimmune responses that are initially primed by APC and stimulated by bystander activation, additional autoantigen-specific T or B cells can be primed through epitope spreading [20], a situation in which an immune response that is initiated by various stimuli, including microbial infection, trauma, transplanted tissue or autoimmunity, spreads to include responses directed against a different portion of the same protein (intramolecular spreading) or a different protein (intermolecular spreading). Activating a broader set of T cells through epitope spreading is helpful in an anti-pathogen or anti-tumour immune response, because the pathogen or tumour cannot easily escape immune control with a single mutation in an immunogenic epitope. However, autoimmune disease potentially arises when spreading cross-reacts with self-proteins, leading to the destruction of self-tissue.

Epitope spreading in animal models proceeds in an orderly and hierarchical manner, such that more immunodominant epitopes elicit responses first, followed by less dominant responses. This type of spreading has been shown in experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis [61,62], as well as in the non-obese diabetic (NOD) mouse model of type 1 diabetes [63]. These examples document epitope spreading within autoantigens and to additional autoantigens.

Mycobacterium leprae is known to preferably reside in Schwann cells. Antibodies to neuronal glycolipids such as galactocerebroside [64,65], ceramide [64] and asialo GM1 of myelin may be associated with nerve damage in leprosy patients. Anti-ceramide IgM antibody titre was significantly higher in multibacillary leprosy patients in comparison to both controls and paucibacillary leprosy patients [66].

An even broader form of bystander activation is achieved by cross-linking MHC class II molecules on APC with TCR comprising a certain V β domain by superantigens. T-cell populations that are stimulated in this manner could potentially contain a subset of T cells specific for a self-antigen [67]. There are multiple examples in which superantigens are involved in diseases such as EAE, arthritis and inflammatory bowel disease, making superantigens another mechanism by which bystander activation can initiate,

or at the least exacerbate, autoimmunity in mouse models [68-70].

Although molecular mimicry might initially prime autoreactive T cells, these responses could be amplified by superantigen-mediated expansion and by activation of autoantigen-specific T cells that express a given V β chain that is targeted by microbial superantigens.

Others mechanisms

Infections can affect the immune response in many ways, and mechanisms such as molecular mimicry and bystander activation are certainly not the only ways in which pathogens might trigger or accelerate autoimmune disease. Infection may lead to autoimmunity through the processing and presentation of cryptic antigens. In contrast to dominant antigenic determinants, subdominant cryptic antigens are normally invisible to the immune system. The inflammatory environment that arises after infection can induce increased protease production and differential processing of released self-epitopes by APC [71].

A recent study showed that in a spontaneous animal model of systemic lupus erythematosus, lipid raft aggregation on T cells, induced by Cholera toxin B from *Vibrio cholerae*, enhanced T-cell signalling and exacerbated systemic lupus erythematosus activity [72].

Persistent infection of microglia with TMEV has been shown to cause upregulation of MHC and costimulatory molecules and enhance the ability of these cells to function as effective APC [73]. This shows that viral infections could also directly maintain autoreactive effector cells or autoantigen-presenting cells.

The fact that the various mechanisms for infection-induced autoimmunity discussed here are interrelated and non-mutually exclusive make them both more complicated and more plausible as potential causes for human autoimmune disease. For example, molecular mimicry and adjuvant effects of pathogens might work early on during the development of autoimmune responses, whereas bystander activation and epitope spreading through the inflammatory environment of infections and/or superantigens might exacerbate autoimmune responses later on [13,26,31,74].

Induction of overt autoimmune disease

Although several causal relationships between pathogen infection and autoimmunity have been

identified in animal models and correlations have been drawn in human autoimmune diseases, pathogen-derived triggers of autoimmunity have been difficult to identify because evidence of autoimmunity is likely to become clinically apparent only after a considerable period of subclinical autoimmune responses.

Autoreactive adaptive immune cells are unavoidably present in the periphery in humans and animals. These cells can exist because their cognate self-antigen was not expressed in the thymus and the antigen will therefore only become apparent to the immune system after tissue destruction as a result of infection or trauma. Alternatively, whereas many autoreactive T cells are deleted in the thymus during development, some T cells that make their way to the periphery might be highly specific for a microbial antigen, but also have lesser affinity for a self-antigen. The presence of autoreactive cells in the periphery, however, does not necessarily predispose for clinical autoimmune disease.

It is clear that, in many cases, an infection is necessary for the development of overt disease, even when abundant autoreactive T cells are present. The potential for the development of overt disease is clearly dependent on the presence of autoreactive T cells. However, whether overt disease actually occurs can depend on various other coincident events, including the number of autoreactive T cells present, the avidity and affinity of these cells (determined by co-receptor expression and binding to MHC/peptide complexes, respectively), and the presence of innate inflammatory signals required for activation and differentiation of those T cells to a pathogenic phenotype. Despite the requirement for all these elements, it is clear that they do not need to happen at the same time or in the same place to elicit autoimmune disease. In many animal models, autoimmune responses are triggered during the initial or acute response to an infection, and autoimmune disease occurs exclusively in the infected organ, such as during corneal HSV infection leading to stromal keratitis [13,30,31]. However, none of the proposed mechanisms for the development of infection-induced autoimmunity excludes the possibility that disease can occur temporally and/or spatially distal from the site of the initiating infection. Animal models that allow investigators to study this aspect of infection-induced autoimmunity are few, but they might provide important insights relevant to human disease. Autoimmune CNS demyelinating disease can be triggered by molecular mimicry when the pathogen containing the mimic epitope does not infect the CNS

itself. When mice that express an LCMV protein in the CNS were peripherally infected with LCMV, autoimmune responses occurred in the CNS despite the fact that LCMV was not detectable in that organ [75].

Finally it is of interest to emphasize that the preferential homing of primed antiviral or antibacterial T cells might also falsely implicate pathogens in the immunopathology of autoimmune diseases. Lytic EBV infection was suspected to contribute to rheumatoid arthritis after it was found that lytic EBV antigen-specific T cells were enriched in inflamed joints [76]. It was later found that these lytic EBV antigenspecific T cells were home to a variety of autoimmune inflamed tissues [77], including knees affected by rheumatoid arthritis, eyes of patients with uveitis, and the brains of patients with multiple sclerosis. These data were interpreted as primarily reflecting the migration of EBV-specific T cells in response to inflammatory chemokines, such as the CXCR3 ligand CXCL10, rather than a direct involvement of EBV-directed immunity in the immunopathology of the autoimmune diseases.

Conclusions

Besides genetic predisposition to autoimmunity, environmental factors are known to be involved in the initiation and promotion of autoimmune diseases. Among these, viral and bacterial infections are the main candidate environmental factors due to their capacity to elicit strong immune activation and to induce autoimmune diseases in animal models, as well as the correlation of several pathogens with autoimmune diseases in humans. These studies suggest that pathogens can trigger autoimmunity through molecular mimicry and their adjuvant effects during initiation of disease, and can promote autoimmune responses through bystander activation or epitope spreading via inflammation and/or superantigens. However, an association of dysregulated antiviral immune responses with a given autoimmune disease has to be interpreted with caution, because these can be differently primed in individuals with ongoing autoimmune disease or with a genetic predisposition to autoimmune disease. Furthermore, the autoimmune disease can alter virus infection by affecting its host cells, and might lead to redistribution of antiviral lymphocytes to sites of autoreactive tissue inflammation.

Dedication

The news that you never want to hear: the passing of a good friend, mentor and scientist. Gianfranco Del Prete said goodbye to this world in November 2010.

Here we would like to remember Gianfranco Del Prete not just because he was a full professor of medicine in the University of Florence or because of his large number of important publications in the immunology field, where one of his major research goals of was the study of important scientific issues related to developing countries. Here we would like to remember Gianfranco as a person able to dedicate himself to research, until the end of his life, with always a very impressive energy, passion and curiosity. He was straightforward but always honest and he had the gift of being able to involve everyone in a magical feeling: the feeling of science ... where you think that with your job, your mind, doing research, working hard with passion, you can improve someone else's life ... you can give new knowledge to the community. A fruitful life of achievement makes Gianfranco Del Prete a Man to be remembered in science.

For all you gave us and to the world it is with great emotion that we say, *Thank you, Gianfranco!*

References

1. Samaras V, Rafailidis PI, Mourtzoukou EG, Peppas G, Falagas ME (2010) Chronic bacterial and parasitic infections and cancer: a review. *J Infect Dev Ctries* 4: 267-281.
2. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Coglianò V (2009) A review of human carcinogens--Part B: biological agents. WHO International Agency for Research on Cancer Monograph Working Group. *Lancet Oncol* 10: 321-322.
3. zur Hausen H (2006) Streptococcus bovis: causal or incidental involvement in cancer of the colon? *Int J Cancer* 119: xi-xii.
4. Rioux JD and Abbas AK (2005) Paths to understanding the genetic basis of autoimmune disease. *Nature* 435: 584-589.
5. Björnsen P, Aaltonen J, Horelli-Kuitunen N, Yaspo ML, Peltonen L (1998) Gene defect behind APECED: a new clue to autoimmunity. *Hum Mol Genet* 7: 1547-1553.
6. Walker LS and Abbas AK (2002) The enemy within: keeping self-reactive T cells at bay in the periphery. *Nat Rev Immunol* 2: 11-19.
7. Münz C, Lünemann JD, Getts MT, Miller SD (2009) Antiviral immune responses: triggers of or triggered by autoimmunity? *Nat Rev Immunol*; 9: 246-258.
8. Selgrade MK, Cooper GS, Germolec DR, Heindel JJ (1999) Linking environmental agents and autoimmune disease: an agenda for future research. *Environ Health Perspect*; 107 (Suppl. 5): 811-813.
9. Rose NR and Bona C (1993) Defining criteria for autoimmune diseases (Witebsky's postulates revisited). *Immunol Today* 14: 426-430.
10. Oldstone MBA (1998) Molecular mimicry and immune mediated diseases. *FASEB J* 12: 1255-1265.
11. Theofilopoulos AN, and Kono DH (1998) Mechanisms and genetics of autoimmunity. *Ann NY Acad Sci* 841: 225-235.
12. Lori JA and Inman RD (1999) Molecular mimicry and autoimmunity. *N Engl J Med* 341: 2068-2074.
13. Benoist C and Mathis D (2001) Autoimmunity provoked by infection: how good is the case for T cell epitope mimicry? *Nat Immunol* 2: 797-801.

14. Wucherpfennig KW (2001) Mechanisms for the induction of autoimmunity by infectious agents. *J Clin Invest* 108: 1097-1104.
15. Bachmaier K, Neu N, de la Maza LM, Pal S, Hessel A, Penninger JM (1999) Chlamydia infections and heart disease linked through antigenic mimicry. *Science* 283: 1335-1339.
16. Rose NR and Mackay IR (2000) Molecular mimicry: a critical look at exemplary instances in human diseases. *Cell Mol Life Sci* 57: 542-551.
17. Hemmer B, Gran B, Zhao Y, Marques A, Pascal J, Tzou A, Kondo T, Cortese I, Bielekova B, Straus SE, McFarland HF, Houghten R, Simon R, Pinilla C, Martin R (1999) Identification of candidate T-cell epitopes and molecular mimics in chronic Lyme disease. *Nat Med* 5: 1375-1382.
18. Martin R, Gran B, Zhao Y, Markovic-Plese S, Bielekova B, Marques A, Sung MH, Hemmer B, Simon R, McFarland HF, Pinilla C (2001) Molecular mimicry and antigen-specific T cell responses in multiple sclerosis and chronic CNS Lyme disease. *J Autoimmun* 16: 187-192.
19. Murali-Krishna K, Altman JD, Suresh M, Sourdive DJ, Zajac AJ, Miller JD, Slansky J, Ahmed R (1998) Counting antigen-specific CD8 T cells: a reevaluation of bystander activation during viral infection. *Immunity* 8: 177-187.
20. Lehmann PV, Forsthuber T, Miller A, Sercarz EE (1992) Spreading of T-cell autoimmunity to cryptic determinants of an autoantigen. *Nature* 358: 155-157.
21. Miller SD, Vanderlugt CL, Begolka WS, Pao W, Yauch RL, Neville KL, Katz-Levy Y, Carrizosa A, Kim BS (1997) Persistent infection with Theiler's virus leads to CNS autoimmunity via epitope spreading. *Nat Med* 3: 1133-1136.
22. Scher MT, Ignatowicz L, Winslow GM, Kappler JW, Marrack P (1993) Superantigens: bacterial and viral proteins that manipulate the immune system. *Annu Rev Cell Biol.* 9: 101-128.
23. Ishii KJ, Koyama S, Nakagawa A, Coban C, Akira S (2008) Host innate immune receptors and beyond: making sense of microbial infections. *Cell Host Microbe* 3: 352-363.
24. Marrack P, Scott-Browne JP, Dai S, Gapin L, Kappler JW (2008) Evolutionarily conserved amino acids that control TCR-MHC interaction. *Annu Rev Immunol* 26: 171-203.
25. Fujinami RS, Oldstone MB, Wroblewska Z, Frankel ME, Koprowski H (1983) Molecular mimicry in virus infection: crossreaction of measles virus phosphoprotein or of herpes simplex virus protein with human intermediate filaments. *Proc Natl Acad Sci USA* 80: 2346-2350.
26. Fujinami RS and Oldstone MB (1985) Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. *Science* 230: 1043-1045.
27. Wucherpfennig KW and Strominger JL (1995) Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. *Cell* 80: 695-705.
28. Lang HL, Jacobsen H, Ikemizu S, Andersson C, Harlos K, Madsen L, Hjorth P, Sondergaard L, Svejgaard A, Wucherpfennig K, Stuart DI, Bell JI, Jones EY, Fugger L (2002) A functional and structural basis for TCR cross-reactivity in multiple sclerosis. *Nat Immunol* 3: 940-943.
29. Gregersen JW, Kranc KR, Ke X, Svendsen P, Madsen LS, Thomsen AR, Cardon LR, Bell JI, Fugger L (2006) Functional epistasis on a common MHC haplotype associated with multiple sclerosis. *Nature* 443: 574-577.
30. Zhao ZS, Granucci F, Yeh L, Schaffer PA, Cantor H (1998) Molecular mimicry by herpes simplex virustype 1: autoimmune disease after viral infection. *Science* 279: 1344-1347.
31. Deshpande SP, Lee S, Zheng M, Song B, Knipe D, Kapp JA, Rouse BT (2001) Herpes simplex virus-induced keratitis: evaluation of the role of molecular mimicry in lesion pathogenesis. *J Virol* 75: 3077-3088.
32. Honeyman MC, Stone NL, Falk BA, Nepom G, Harrison LC (2010) Evidence for molecular mimicry between human T cell epitopes in rotavirus and pancreatic islet autoantigens. *J Immunol* 184: 2204-2210.
33. Agabi YA, Banwat EB, Mawak JD, Lar PM, Dashe N, Dashen MM, Adoga MP, Agabi FY, Zakari H (2010) Seroprevalence of herpes simplex virus type-2 among patients attending the Sexually Transmitted Infections Clinic in Jos, Nigeria. *J Infect Dev Ctries* 4: 572-575.
34. Cunningham MW, Antone SM, Gulizia JM, McManus BM, Fischetti VA, Gauntt CJ (1992) Cytotoxic and viral neutralizing antibodies crossreact with streptococcal M protein, enteroviruses, and human cardiac myosin. *Proc Natl Acad Sci U S A* 89: 1320-1324.
35. Christen U, Edelman KH, McGavern DB, Wolfe T, Coon B, Teague MK, Miller SD, Oldstone MB, von Herrath MG (2004) A viral epitope that mimics a self-antigen can accelerate but not initiate autoimmune diabetes. *J Clin Invest* 114: 1290-1298.
36. Mokhtarian F, Zhang Z, Shi Y, Gonzales E, Sobel RA (1999) Molecular mimicry between a viral peptide and a myelin oligodendrocyte glycoprotein peptide induces autoimmune demyelinating disease in mice. *J Neuroimmunol* 95: 43-54.
37. Gauntt CJ, Arizpe HM, Higdon AL, Wood HJ, Bowers DF, Rozek MM, Crawley R (1995) Molecular mimicry, anti-coxsackievirus B3 neutralizing monoclonal antibodies, and myocarditis. *J Immunol* 154: 2983-2995.
38. Lawson CM (2000) Evidence for mimicry by viral antigens in animal models of autoimmune disease including myocarditis. *Cell Mol Life Sci* 57: 552-560.
39. Yurasov S, Wardemann H, Hammersen J, Tsuiji M, Meffre E, Pascual V, Nussenzweig MC (2005) Defective B cell tolerance checkpoints in systemic lupus erythematosus. *J Exp Med* 201: 703-711.
40. Samuels J, Ng YS, Coupillaud C, Paget D, Meffre E (2005) Impaired early B cell tolerance in patients with rheumatoid arthritis. *J Exp Med* 201: 1659-1667.
41. Lovett-Racke AE, Trotter JL, Lauber J, Perrin PJ, June CH, Racke MK (1998) Decreased dependence of myelin basic protein-reactive T cells on CD28-mediated costimulation in multiple sclerosis patients. A marker of activated/memory T cells. *J Clin Invest* 101: 725-730.
42. Markovic-Plese S, Cortese I, Wandinger KP, McFarland HF, Martin R (2001) CD4+CD28- costimulation independent T cells in multiple sclerosis. *J Clin Invest* 108: 1185-1194.
43. Baranzini SE, Jeong MC, Butunoi C, Murray RS, Bernard CC, Oksenberg JR (1999) B cell repertoire diversity and clonal expansion in multiple sclerosis brain lesions. *J Immunol* 163: 5133-5144.
44. Babbe H, Roers A, Waisman A, Lassmann H, Goebels N, Hohlfeld R, Friese M, Schröder R, Deckert M, Schmidt S, Ravid R, Rajewsky K (2000) Clonal expansions of CD8+ T cells dominate the T cell infiltrate in active multiple sclerosis lesions as shown by micromanipulation and single cell polymerase chain reaction. *J Exp Med* 192: 393-404.
45. Skulina C, Schmidt S, Dornmair K, Babbe H, Roers A, Rajewsky K, Wekerle H, Hohlfeld R, Goebels N (2004)

- Multiple sclerosis: brain-infiltrating CD8+ T cells persist as clonal expansions in the cerebrospinal fluid and blood. *Proc Natl Acad Sci U S A* 101: 2428-2433.
46. Meinl E, Weber F, Drexler K, Morelle C, Ott M, Saruhan-Direskeneli G, Goebels N, Ertl B, Jechart G, Giegerich G (1993) Myelin basic protein-specific T lymphocyte repertoire in multiple sclerosis. Complexity of the response and dominance of nested epitopes due to recruitment of multiple T cell clones. *J Clin Invest* 92: 2633-2643.
 47. Goebels N, Hofstetter H, Schmidt S, Brunner C, Wekerle H, Hohlfeld R (2000) Repertoire dynamics of autoreactive T cells in multiple sclerosis patients and healthy subjects: epitope spreading versus clonal persistence. *Brain* 123: 508-518.
 48. Muraro PA, Wandinger KP, Bielekova B, Gran B, Marques A, Utz U, McFarland HF, Jacobson S, Martin R (2003) Molecular tracking of antigen-specific T cell clones in neurological immunemediated disorders. *Brain* 126: 20-31.
 49. Thacker EL, Mirzaei F, Ascherio A (2006) Infectious mononucleosis and risk for multiple sclerosis: a metaanalysis. *Ann Neurol* 59: 499-503.
 50. Nielsen TR, Rostgaard K, Nielsen NM, Koch-Henriksen N, Haahr S, Sørensen PS, Hjalgrim H (2007) Multiple sclerosis after infectious mononucleosis. *Arch Neurol* 64: 72-75.
 51. Nielsen TR, Rostgaard K, Askling J, Steffensen R, Oturai A, Jersild C, Koch-Henriksen N, Sørensen PS, Hjalgrim H (2009) Effects of infectious mononucleosis and HLA-DRB1*15 in multiple sclerosis. *Mult Scler* 15: 431-436.
 52. Lünemann JD, Jelčić I, Roberts S, Lutterotti A, Tackenberg B, Martin R, Münz C (2008) EBNA1-specific T cells from patients with multiple sclerosis cross react with myelin antigens and co-produce IFN- γ and IL-2. *J Exp Med* 205: 1763-1773.
 53. Toh BH, van Driel IR, and Gleeson PA (1997) Pernicious anemia. *N Engl J Med* 337: 1441-8.
 54. Karlsson FA, Burman P, Loof L, and Mardh S (1988) Major parietal cell antigen in autoimmune gastritis with pernicious anemia is the acid-producing H+K+-adenosine triphosphatase of the stomach. *J Clin Invest* 81: 475-479.
 55. Toh BH, van Driel IR, and Gleeson PA (1992) Autoimmune gastritis: tolerance and autoimmunity to the gastric H+K+ ATPase (proton pump). *Autoimmunity* 13: 165-172.
 56. D'Elis MM, Bergman MP, Azzurri A, Amedei A, Benagiano M, De Pont JJ, Cianchi F, Vandenbroucke-Grauls CM, Romagnani S, Appelmelk BJ, and Del Prete G (2001) H+K+-ATPase (proton pump) is the target autoantigen of Th1-type cytotoxic T cells in autoimmune gastritis. *Gastroenterology* 120: 377-386.
 57. Yamaoka Y (2008) Increasing evidence of the role of *Helicobacter pylori* SabA in the pathogenesis of gastroduodenal disease. *J Infect Dev Ctries* 2: 174-1781.
 58. Amedei A, Bergman MP, Appelmelk BJ, Azzurri A, Benagiano M, Tamburini C, van der Zee R, Telford JL, Vandenbroucke-Grauls CM, D'Elis MM, Del Prete G (2003) Molecular mimicry between *Helicobacter pylori* antigens and H+, K+ -adenosine triphosphatase in human gastric autoimmunity. *J Exp Med* 198: 1147-1156.
 59. Zipris D, Lien E, Xie JX, Greiner DL, Mordes JP, Rossini AA (2005) TLR activation synergizes with Kilham rat virus infection to induce diabetes in BBDR rats. *J Immunol* 174: 131-142.
 60. Walker LS, Abbas AK (2002) The enemy within: keeping self-reactive T cells at bay in the periphery. *Nat Rev Immunol* 2: 11-19.
 61. McRae BL, Vanderlugt CL, Dal Canto MC, Miller SD (1995) Functional evidence for epitope spreading in the relapsing pathology of experimental autoimmune encephalomyelitis. *J Exp Med* 182: 75-85.
 62. Yu M, Johnson JM, Tuohy VK (1996) A predictable sequential determinant spreading cascade invariably accompanies progression of experimental autoimmune encephalomyelitis: a basis for peptidespecific therapy after onset of clinical disease. *J Exp Med* 183: 1777-1788.
 63. Kaufman DL, Clare-Salzler M, Tian J, Forsthuber T, Ting GS, Robinson P, Atkinson MA, Sercarz EE, Tobin AJ, Lehmann PV (1993) Spontaneous loss of T-cell tolerance to glutamic acid decarboxylase in murine insulin-dependent diabetes. *Nature* 366: 69-72.
 64. Cho SN, Gormus BJ, Xu K, Bohm RP Jr., Walsh GP, Meyers WM, Kim JD (1993) Serologic responses to nerve antigens in sooty mangabey monkeys with experimental leprosy. *Int J Lep Other Mycobact Dis* 61: 236-244.
 65. Kim JD, Cho SN, Park S, Walsh GP (1997) Detection of antibodies to nerve antigens in sera from leprosy patients and relevance to the nerve damage. *Korean J Immunol* 19: 463-70.
 66. Singh K, Singh B, Ray PC (2010) Anti-ceramide antibodies in leprosy: marker for nerve damage? *J Infect Dev Ctries* 4: 378-381.
 67. Wucherpfennig KW (2001) Mechanisms for the induction of autoimmunity by infectious agents. *J Clin Invest* 108: 1097-1104.
 68. Brocke S, Gaur A, Piercy C, Gautam A, Gijbels K, Fathman CG, Steinman L (1993) Induction of relapsing paralysis in experimental autoimmune encephalomyelitis by bacterial superantigen. *Nature* 365: 642-644.
 69. Cole BC and Griffiths MM (1993) Triggering and exacerbation of autoimmune arthritis by the *Mycoplasma arthritidis* superantigen MAM. *Arthritis Rheum* 36: 994-1002.
 70. Dalwadi H, Wei B, Kronenberg M, Sutton CL, Braun J (2001) The Crohn's disease-associated bacterial protein I2 is a novel enteric T cell superantigen. *Immunity* 15: 149-158.
 71. Ercolini AM and Miller SD (2008) The role of infections in autoimmune disease. *Clin Exp Immunol* 155: 1-15.
 72. Deng GM and Tsokos GC (2008) Cholera toxin B accelerates disease progression in lupus-prone mice by promoting lipid raft aggregation. *J Immunol* 181: 4019-4026.
 73. Olson JK, Ludovic Croxford J, Miller SD (2004) Innate and adaptive immune requirements for induction of autoimmune demyelinating disease by molecular mimicry. *Mol Immunol* 40: 1103-1108.
 74. Fujinami RS, von Herrath MG, Christen U, Whitton JL (2006) Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. *Clin Microbiol Rev* 19: 80-94.
 75. Evans CF, Horwitz MS, Hobbs MV, Oldstone MB (1996) Viral infection of transgenic mice expressing a viral protein in oligodendrocytes leads to chronic central nervous system autoimmune disease. *J Exp Med* 184: 2371-2384.
 76. Scotet E, David-Ameline J, Peyrat MA, Moreau-Aubry A, Pinczon D, Lim A, Even J, Semana G, Berthelot JM, Breathnach R, Bonneville M, Houssaint E (1996) T cell response to Epstein-Barr virus transactivators in chronic rheumatoid arthritis. *J Exp Med* 184: 1791-1800.

77. Scotet E, Peyrat MA, Saulquin X, Retiere C, Couedel C, Davodeau F, Dulphy N, Toubert A, Bignon JD, Lim A, Vie H, Hallet MM, Liblau R, Weber M, Berthelot JM, Houssaint E, Bonneville M (1999) Frequent enrichment for CD8 T cells reactive against common herpes viruses in chronic inflammatory lesions: towards a reassessment of the physiopathological significance of T cell clonal expansions found in autoimmune inflammatory processes. *Eur J Immunol* 29: 973-985.

Corresponding author

Roberto Manetti, MD
Department of Clinical, Experimental and Oncological Medicine
University of Sassari
8 Viale San Pietro, 07100 Sassari, Italy
Telephone: +39 (079) 229014,
Fax: +39 (079) 228207
Email: rmanetti@uniss.it

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