Autoimmunity review pdf

Autoimmune disease has proven to be a unique conceptual and medical challenge, but the hope of effective targeted therapies is very close. Editorial | June 20th, 2018 | Nature Immunology The scam plays a critical role in establishing adequately educated and self-indefit tolerant T cells. In their Focus Review, Cheng and Anderson talk about the latest ideas about how the scam establishes self-tolerance. Mickie Cheng &; Mark S. Anderson Article Review | June 20th, 2018 | Nature Immunology Treg cells play a critical role in maintaining peripheral tolerance. In this Focus Review, Domínguez-Villar and Hafler describe how the instability and plasticity of Treg cells can contribute to the breakdown of tolerance and lead to autoimmune diseases. Margarita Domínguez-Villar && David A. Hafler Review Article | June 20th, 2018 | Nature immunology Autoimmune disease has been the subject of intense genetic study. In this Focus Review, Todd and colleagues describe recent advances and approaches in the genetic analysis of autoimmune disease. Jamie R. J. Inshaw, Antony J. Cutler ⋯ John A. Todd Review Article | June 20th, 2018 | Nature Immunology Rates of autoimmune disease are rising faster than can be explained by changes in genetics. In this Focus Review, Verdu and Danska describe dietary and microbial influences on type 1 diabetes and draw comparisons with celiac disease. Elena F. Verdu && Jayne S. Danska Review Article | June 20th, 2018 | Nature Immunology In this Focus Review, Bar-Or and colleagues discuss the latest evidence that B cells play an important role independent of antibodies in multiple sclerosis and the prospects this has for therapeutic intervention. Rui Li, Kristina R. Patterson & Amit Bar-Or Review Article | June 20th, 2018 | Nature Immunology A conversation with Shawn Rose, Director of Immunology Global Clinical Development, Janssen Research & Development, LLC Advertising Feature | 11 June 2018 Jason D. Fontenot, Marc A. Gavin & Alexander Y. Rudensky Article | March 3rd, 2003 | Nature immunology CD4 + T cell tolerance can be applied by various mechanisms. Jenkins and colleagues used mice with fully intact polycclonal cell repertoire to comprehensively define the mechanisms of self tolerance. Deepali Malhotra, Jonathan L Linehan ⋯ Marc K Jenkins Article | January 4, 2016 | Nature immunology The development of experimental autoimmune encephalomyelitis has been attributed to cells in subset TH1 or TH17 of helper T cells. Becher and Rostami and their colleagues show that IL-23-induced production of GM-CSF cytokine underlying the development of disease and severity. Laura Codarri, Gabor Gyülvészi ⋯ Burkhard Becher Article | April 24th, 2011 | The immunology of nature autoimmunity when the mechanisms of tolerance break down. Theofilopoulos and colleagues review how the loss of peripheral tolerance, often driven by innate nucleic-acid sensors, leads to the activation of self-active lymphocytes that underlying many autoimmune diseases. Argyrios N Theofilopoulos, Dwight Dwight Kono && Roberto Baccala Article Review | 20 June 2017 | Nature Immunology Review articleAbstract onlyGreta Pacini, ... Maurizio CutoloIn Press, Corrected Test, Available online October 22 2020Buy PDF access text text aFaraz S. Hussain, ... Zaeem A. SiddiqiIn Press, Pre-Trial Journal, Available online October 22 2020 Download PDF articleAbstract onlyMario Bautista-Vargas, ... Gabriel J. TobónIn Press, Pre-trial Magazine, Available online October 22 2020Buy PDF accessOsa Bruscolini, ... Marta SacchettiIn Press, Pre-trial Magazine, Available online October 22 2020Buy PDF accessDenis Miyashiro, ... José Antonio SanchesIn Press, Daily Pre-Test, Available Online October 22 2020Buy PDF articleAbstractar onlyAline G. Islabão, ... Clovis A. SilvaIn Press, Pre-trial Journal, Available online October 22, 2020Buy PDF articleAbstract onlyGilberto Pires da Rosa, ... Gerard EspinosaIn Press, Daily Pre-Test, Available Online 22 October 2020Buy PDF articleAbstract onlyYue Shi, ... Xiaofeng ZengIn Press, Daily Pre-Test, Available Online October 22, 2020Buy PDF search form ©2020 VIVO Project | Terms of Use | Developed by VIVO Because most patients with autoimmune disease develop symptoms long after abnormal immune reactions begin, it is often difficult to identify the factors responsible for the initiation of the disease. Although animal models are informative, in fact there are few models of spontaneous autoimunity that reliably mimic human disorders. However, studies using existing models, as well as genetic and other analyses, begin to reveal some of the anomalies that represent the first steps in the autoimmune reaction. Autoimmune diseases, like many other complex disorders, are thought to arise from a combination of genetic and environmental factors. A simple hypothesis is that polymorphisms in several genes give rise to a faulty regulation or reduced threshold for the activation of lymphocytes, and environmental factors initiate or increase the activation of self-reactive lymphocytes that have escaped control and are willing to react against self-confessaments (Figure 2). Some of these genetic factors and environmental influences begin to be identified. Figure 2Suceptibility genetics, environmental stimuli and faulty regulation are responsible for initiateing autoimunity. Genetic polymorphisms in immune genes (including HLA, cytokine/receptors, and those involved in central) can lower the threshold for the activation of self-reactive T cells. Environmental triggers such as the microbiome, and tissue injury generate a pro-inflammatory environment that supports the activation of self-active lymphocytes. Tregs typically work to suppress self-active T cells, but defects in development, stability or function can cause these dysfunctional cells and cannot control the responses of self-reactive T cells. Alone or in combination, these factors can contribute to the escape, activation and proliferation of self-active lymphocytes that give rise to tissue injuries and clinical diseases. Genetic susceptibility to autoimmune diseases. A large number of association studies throughout the genome have suggested a role for numerous genetic polymorphisms in different autoimmune diseases (3, 4). Most polymorphisms are found in gene-regulating regions whose products are believed to play roles in immune responses. The contribution of each gene to a particular disease, as indicated by the probability ratio, is small, and multiple polymorphisms are likely to contribute to the development of diseases in individual patients. However, it has been difficult to define the role of most of these polymorphisms in the breakdown of tolerance to autoantígens and the development of autoimunity. For example, of all the genes associated with autoimmune diseases, the strongest associations and the ones that have been known for longer, are with particular HLA allerles (5). However, it is not yet definitively known how different HLA alleu contribute to any autoimmune disease. It is unlikely that an allergen associated with the disease is especially efficient in showing autoantygens directed by autoactive T cells because most HLA allergens are able to present autoantygens even in healthy individuals. In addition, most healthy individuals have self-reactive T cells that escape from thymic suppression (6, 7). The problem of using the knowledge of the genes involved to elucidate the pathogenesis of autoimmune diseases is much more daunting for other polymorphisms with much lower probability ratios than those of hla allele. Genetic polymorphisms receptors of cytokine and cytokine have been linked to many different autoimmune diseases. Perhaps the best example of this is IL23R. IL-23 is a cytokine that increases the pro-inflammatory capacity of Th17 cells (8). Genetic polymorphisms in IL23R have been discovered in ankylative spondylitis, Behcet disease, Crohn's disease, psoriasis and ulcerative colitis (9). Consequently, Th17 inflammatory cells have been associated with tissue damage in all these diseases, and targeting these pathways with p40-specific monoclonal antibodies (a subunit of IL-23) or IL-17A has proven effective in almost all of these disorders (10, 11). Thus, genetic polymorphisms in IL23R have been correlated with responses to targeted anticytocin therapies. While a predisposition to develop most human autoimmune diseases is thought to be the result of multi-gene polymorphisms involved in immune function, there are rare examples in which genetic alterations in a single gene give rise to fulminating autoimunity. Perhaps the two best examples of monogenetic autoimmune diseases are autoimmune polyendocrine syndrome (APS) and X-linked immunodisgulation polyendocrinology enteropathy syndrome (IPEX). These diseases are the direct result of mutations in AIRE and FOXP3, respectively (12, 13), leading to catastrophic dysfunction in central and peripheral tolerance (IPEX). Another example is autoimmune lymphofiferant syndrome, a rare lymphatic disorder caused by mutations in fas or fas lligand, or in caspases downstream of fas signage. These mutations give rise to a defective apoptotic pathway mediated by fas and chronic lymphoproliferation causing lymphadenopathy, splenomegaly and autoimmune cytopenia (14). The discovery of the unique genes responsible for these disorders has contributed greatly to our understanding of the cell and molecular pathways that are dysfunctional in many autoimmune diseases. Environmental triggers of autoimunity. It has long been suspected that infections trigger autoimmune reactions (15, 16). Multiple theories have been proposed to explain this association, including the spread of

epitopes, antigenic complementarity and excessive activation of the innate/pattern recognition receptor. For example, evidence of EBV infection in post-mortem brain tissue has been associated with MS, but not other inflammatory disorders (17). In addition, it has been reported that systemic infections trigger relapses in patients with MS who relapse through improved specific T-cell responses of muslin (15). Another example of the association of autoimmune infections is periodontal infections and rheumatoid arthritis (18). However, infections are also postulated to protect against some autoimmune diseases. For example, it has been reported the infection of germ-free mice with frail bacteroids to protect against experimental autoimmune encephalomyelitis, the mouse model of MS, by inducing Treg cells (19). In addition, a higher incidence of ME and type 1 diabetes correlates with a decrease in the number of infections in developed countries (20). Recent interest has focused on the possible role of the microbiome in influencing local and systemic immune responses. Much of the emphasis has been on the gut microbiome. It is now believed that inflammatory bowel disease (IBS) is initiated through disregulated and exaggerated immune responses to intestinal commensal microbes. In fact, the main manifestations of MII can be caused by antimicrorocial immune reactions and not by a true autoimmunity (i.m. aimed at tissue autoantygens). There are also several studies in mice involving commensal microbes in diseases including type 1 diabetes (revised in ref. 21). A well-recognized nomicrobial environmental trigger is UV irradiation for skin lupus. One possible explanation for this connection is that UV radiation induces of many cell types and increases the burden of nuclear antigens, especially if dead cells cannot be cleaned efficiently (22). It has been suggested that the death of low-level natural cells in tissues is a mechanism to maintain peripheral tolerance to tissue antigens through populations of dendrotic cells that promote tolerance (23). It is plausible that lupus patients have a genetic predisposition so that this system is easily overflowing and, therefore, they cannot maintain tolerance in the presence of continuous UV exposure. Faulty regulation as a cause of autoimunity. If the failure of self tolerance is the fundamental abnormality in autoimmune diseases, the central question becomes - what mechanisms of tolerance fail in specific diseases, and why? In patients with SLE, defects have been proposed in the suppression of immature B cells in the bone marrow, in the editing of receptors, and in the control of mature B cells in peripheral tissues (24). In humans with SLE, mature naïve B cells can produce autoantibodies even before encountering the antigen, suggesting that defects in the first B cell tolerance controls may contribute to disease development (24). In inflammatory autoimmune diseases dependent on T cells, there is likely to be an imbalance between t-cells and functional Treg cells. Autoimmune mouse models support the pathogenic importance of this imbalance (25). It also seems likely to decrease in the number of functional Tregs, or the resistance of T cells effect to regulation, play a role in the initiation of human autoimmune disease. However, data from patients with different autoimmune diseases tend to be variable and often inconsistent. This is probably due to the fact that for most autoimmune diseases, Treg cells work in tissue led by the autoimmune process (not in the blood) and mechanical studies are difficult to perform with these cell populations, given the limited accessibility of human tissue. In addition, when you get an adequate number of these cells, their function (or lack thereof) is usually evaluated by in vitro trials that may not accurately recap their functional capacity in vivo. Longitudinal studies of effector and Treg cells specific to target autoantygens in human diseases remain a considerable technical challenge. It is not obvious that population trials will discover defects that, almost by definition, should affect only a small fraction of lymphocyte clones, especially those that are specific to autoantygens involved in specific diseases. In addition to a failure of the regulation underlying the development of autoimmune, other factors have been proposed. There is evidence that autoimmune reactions are associated with abnormalities in the types of auto-antigens shown in the immune system. For example, the atypical presentation of extracellularly derived peptides or denatured proteins by cells that present antigen (APCs) can lead to peptide/MHC complexes that are normally generated within APCs and are therefore able to activate potentially pathogenic T cells (26). This unconventional activation of potentially self-reactive T cells may arise from the recognition of peptide/MHC conformational isomers or a differential binding record of a peptide within the groove of the molecule MHC (27, 28). However, it is not known whether these altered autoantergens are triggers of autoimunity in human diseases. In addition to altered peptide/MHC recognition, an early innate immune response can be a trigger for autoimmune (29). For example, mice that do not have the ubiquity by modifying the enzyme A20 develop lethal autoimmune due to independent MyD88 TLR signals (30). In addition, Yaa mice, which have a genetic duplication of Tlr7, develop spontaneous SLE-shaped syndrome due to increased B cell recognition of nucleolar antigens (31). The contribution of excessive or aberrant innate immune responses to human autoimmune diseases is yet to be defined. Despite our current lack of understanding of the initiation of autoimmune disease in humans, models are being pursued that try to recapitulate this process with in vivo human tissue and actively constitute an area of exciting new research. In fact, it has been shown that the seemingly normal skin transplantation of psoriasis patients in immunodeficient mice (i.e. humanized mice) induces skin changes consistent with the initiation of psoriasis (32), and this type of model is currently being explored in other human autoimmune diseases. Diseases.