



Editorial

Participation of T Lymphocytes in the Development and Perpetuation of Rheumatoid Arthritis[☆]

Participación de los linfocitos T en el desarrollo y perpetuación de la artritis reumatoide

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The emphasis on T lymphocytes (TL) as an engine or perpetuating factor in rheumatoid arthritis (RA) has changed over time. The TL constitute the most plastic specific or adaptive immune system cells, both in their ability to recognize different antigens as in their various forms of response. Thus TL are responsible for orchestrating the most powerful and specific defensive responses, but also overall autoimmune responses, them being antigen-specific (autoantigens). However, insufficient identification of autoantigens responsible for autoimmune T-cell responses, particularly in RA, has been a major constraint to understand these responses. While rheumatoid factor and more recently the anti-CCP antibodies (anti-CCP) are well known B responses as well as easy to detect in patients, this does not happen with any T cell response in RA. Some animal models illustrate, however, that it is possible to induce T-dependent arthritis in the absence of antigen-specific T cells by simply expanding or increasing the activation in a poly-specific manner. This occurs, for example, in response to genetic manipulation of factors that amplify global intracellular activation of the TCR receptor (ZAP70) or cytokine receptors (gp130).^{1,2}

Another source of skepticism about T cells dependence in RA was the development of T immunosuppressive drugs and strategies that have proven very effective in preventing transplant rejection, but had little impact on RA therapy. The advent of effective anti-TNF- α , paradoxically a TL activator, moved the attention to innate immune response cells. Despite these questions, two facts strongly support the importance of TL participation in both susceptibility and the development of the disease. The first is related to advances of genetic studies, particularly whole genome studies. Many other associations, whose functional significance point unequivocally to a TL response, have joined the classic association of RA and the shared epitope by different alleles of HLA class II genes. While the shared epitope is the platform for interaction between HLA-antigen for presentation to T-cell receptors (TCR), other genes are known to encode elements such as receptors, or intracellular soluble factors that regulate multiple functions specific to TL.

Of the approximately 30 known susceptibility genes in RA, about half are clearly related to the role of TL.³

Second, at last we have a specific therapy against TL (CTLA4-Ig or abatacept) effective in RA. The only known target of this therapy is the process of costimulation needed for TL activation. This therapy interferes more powerful with the primary T-cell responses to antigens than with memory, challenging the traditional concepts about the importance of memory T cells in RA. In addition, other therapies that are not aimed specifically at TL, such as anti-TNF- α , anti-CD20 or anti-IL6R have had similar success. It seems that once the disease is established, the interdependence of all elements is so strong that the interruption of any of them has a similar effect. There does not seem to exist between these molecular targets or cellular an element which is hierarchically superior to others in the pathogenesis of RA. This is something that never ceases to amaze, as all therapies appear to induce quantitatively similar therapeutic responses (proportion of ACR responders), but also qualitatively in their effects on synovial cell infiltrates, cytokines, vessels, etc., or their final impact on bone and cartilage. The effector TL can induce B autoimmune responses such as arthritis through organ-specific or non-organ-specific antibodies, in this case by means of immune complexes and complement activation. They are also producers of cytokines that activate other effector cells locally such as macrophages or fibroblasts, inducing cartilage and bone destruction factors. Finally, the TL can be induced by direct contact of osteoclast differentiation. The first mechanism seems sufficient to produce RA, at least in patients with auto-antibodies (anti-CCP or RF). There is indirect evidence of the need for cooperation to generate a TL auto-antibody response in RA, but it is difficult to identify. In part this may be due to methodological difficulties. The peripheral blood is not the best place to find a few specific clones of TL. Perhaps the synovial may not be either, and primary or secondary lymphoid compartments (bone marrow or lymph) remaining inaccessible to study in RA. The second mechanism, local, would require the migration of effector TL to the joint, which exert their action via TL cytokines. Among them is IL-17 which has emerged as the most relevant in animal models of arthritis. However, the dependence of human rheumatoid synovitis of the local presence of effector T cells producing IL-17 (Th17) has not yet been fully demonstrated. The study of this kind of response has helped demonstrate the plasticity of human TL in the presence of inflammation. In humans, the re-differentiation of

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one cell response to another, or the existence of mixed responses or Th2/17 Th1/17 seems possible, with no Th1, Th2, Th17 phenotype terminally differentiated cells, but able to adapt and produce interferon-gamma, IL-17, IL-4, etc., depending on the environment. In any case, IL-17 seems an abundant cytokine in RA, perhaps from other T cell sources, and antagonists of IL-17 or other factors related to it show good therapeutic perspectives.^{4,5} Finally, T tolerance induction therapy of RA or other autoimmune diseases is a long sought concept, now with new strategies. Vaccines, cytokines and tolerogenic dendritic cells, mesenchymal stem cells, regulatory T cells (Treg) are some of the strategies under study. Despite their growing popularity, none has advanced beyond open studies or “proof of concept”, so its future is still difficult to predict. However, an important conceptual advance is that many of these elements operate naturally in RA, albeit abnormally or insufficiently to stop the process. An example of an insufficient or abnormal response is related to the Treg, whose number or ability to suppress inflammatory responses and pathological T cells is decreased in RA, and seem to improve in patients who respond to anti-TNF- α .⁶ The purpose

of the reprogramming of the TL as a way toward healing RA still seems far away, but other knowledge on the road is emerging as well as other therapeutic avenues to reward the research effort.

References

1. Sakaguchi N, Takahashi T, Hata H, Nomura T, Tagami T, Yamazaki S, et al. Altered thymic T-cell selection due to a mutation of the ZAP-70 gene causes autoimmune arthritis in mice. *Nature*. 2003;426:454–60.
2. Sawa S, Kamimura D, Jin GH, Morikawa H, Kamon H, Nishihara M, et al. Autoimmune arthritis associated with mutated interleukin (IL)-6 receptor gp130 is driven by STAT3/IL-7-dependent homeostatic proliferation of CD4+ T cells. *J Exp Med*. 2006;203:1459–70.
3. Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP, et al. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. *Nat Genet*. 2010;42:508–14.
4. van den Berg WB, Miossec P. IL-17 as a future therapeutic target for rheumatoid arthritis. *Nat Rev Rheumatol*. 2009;5:549–53.
5. Hueber AJ, Asquith DL, Miller AM, Reilly J, Kerr S, Leipe J, et al. Mast cells express IL-17A in rheumatoid arthritis synovium. *J Immunol*. 2010;184:3336–40.
6. Nadkarni S, Mauri C, Ehrenstein MR. Anti-TNF-alpha therapy induces a distinct regulatory T cell population in patients with rheumatoid arthritis via TGF-beta. *J Exp Med*. 2007;204:33–9.