

**New surrogate markers for autoimmune disease activity.**

D D Patel, B F Haynes

*J Clin Invest.* 1998;**102**(6):1075-1076. <https://doi.org/10.1172/JCI4907>.

Editorial

**Find the latest version:**

<https://jci.me/4907/pdf>



A key issue in understanding the etiology of autoimmunity is the identification of pathogenic cells that cause or contribute to disease activity. Recent breakthroughs in several areas of immunobiology have spawned a new generation of surrogate markers for inflammation that may lead to the identification of pathogenic cells for autoimmune disease. Further, these markers have the potential to lead to novel and more effective ways to predict and monitor disease activity and responses to therapy. The breakthroughs that have occurred include: the understanding of the role of chemokines and adhesion molecules that are necessary for leukocyte extravasation into sites of inflammation; development of intracellular cytokine assays for activated cytokine-producing cells; and the ability to assay for antigen-specific T cells using peptide-loaded, fluorochrome-conjugated MHC tetramers (Table I).

Generally, pathogenic cells for autoimmune disease have been believed to have an activated phenotype manifested by high levels of MHC molecules, cytokine receptors (e.g., CD25, IL-2 receptor  $\alpha$ ), adhesion molecules (e.g., CD44), and cytoplasmic cytokines. Many investigators have shown that the levels of cytokines and soluble adhesion molecules can be elevated in serum, tissue, or bodily fluids during active autoimmune disease, and these assays are being investigated for their utility in the diagnosis or monitoring of autoimmune diseases. Activated T cell subsets can now be identified and monitored by intracellular staining of cytokines using anticytokine mAbs (1). In rheumatoid arthritis, pathogenic T cells may be oligoclonal due to DR4 alleles selecting a potentially autoreactive T cell population (2). The advent of PCR-based analyses of the V $\beta$  repertoire of individuals now makes possible the routine monitoring of TCR clonal changes over time (3), and may allow the identification and monitoring of pathogenic clones of T cells in a variety of autoimmune diseases.

The development of the MHC tetramer technology (wherein tetramers of fluorochrome-labeled, peptide-loaded MHC class I molecules that have a high avidity for cells express the appropriate TCR and are detectable by flow cytometry) has revolutionized the methods to identify antigen-specific CD8<sup>+</sup> T cells (4, 5). This technology is now being applied to evaluate antigen-specific, effector CD8<sup>+</sup> T cells in a variety of diseases, including HIV-1, HTLV-I, and EBV infection. It is likely that MHC class I and/or class II tetramers may be useful in identifying pathogenic T cells in diseases where there are known peptide antigens such as insulin in type 1 diabetes mellitus (6), and the shared epitope of DR4 in rheumatoid arthritis (7).

The development of new surrogate markers such as those described above has broad implications for the diagnosis and monitoring of autoimmune diseases. Current data suggest that activated, circulating, autoreactive cells are pathogenic and ex-

ert their affects in the tissues into which they migrate. However, while cells from patients with autoimmune syndromes have increased expression of activation markers, many of these markers do not correlate well with disease activity.

In this issue of the *Journal*, Estess et al. present data that the rolling activity of T cells on the CD44 ligand hyaluronan (HA), but not the T cell surface expression of activation markers CD25, CD69 or HLA-DR, correlates with disease activity in pediatric patients with SLE or chronic arthropathies (8). These data suggest that pathogenic T cells are functionally activated to migrate into inflamed tissues via CD44-HA interactions. This work also raises the intriguing possibility that pathogenic T cells in SLE and chronic arthropathies may be identified by their ability to bind HA or function in leukocyte rolling assays.

CD44 has been suggested to play a central role in normal leukocyte migration and in autoimmune inflammatory responses (9, 10). Antibodies to CD44 block tissue edema and the migration of inflammatory cells into synovium in proteoglycan-induced arthritis (11). The proinflammatory cytokine TNF- $\alpha$ , central in the pathogenesis of rheumatoid arthritis and inflammatory bowel disease, upregulates HA binding to CD44 in monocytes, and the antiinflammatory cytokines IL-4 and IL-13 downregulate monocyte CD44-HA binding (12). Data presented by Estess et al. (8) suggest that a subset of T cells from patients with active SLE or inflammatory arthritis rolls on HA, and that CD44 on T cells can be activated to bind HA after T cell activation via TCR ligation. Thus, from these studies, pathogenic cells in SLE and chronic arthropathies appear to be T cells that are activated in vivo, possibly by a TCR-mediated activation signal. The ability to identify activated pathogenic T cells in the blood of patients with SLE and in patients with chronic arthritis by their binding to or rolling on HA should provide a powerful new tool that will yield new insights into the pathogenesis of autoimmunity. In addition,

*Table I. Potential Surrogate Markers of Autoimmune Disease Activity for Current and Future Studies*

Surrogate marker	Comment
Serum, tissue, or cavity fluid cytokine or adhesion molecule levels determined by ELISA	Under development
Intracellular T cell cytokine levels determined by flow cytometry	Under development
Antigen-specific T cell levels determined by flow cytometry-based MHC class I or class II tetramer assays	Will require development of appropriate reagents and validation via clinical studies
Analysis of TCR repertoire determined by PCR-based assays	Will require validation via clinical studies
Constitutive function in adhesion molecule or leukocyte migration assays	Will require confirmation, and further development of reagents/assays

studies like that of Estess et al. (8) should help us to develop better surrogate markers of autoimmune disease activity than are currently available for clinical use.

Dhavalkumar D. Patel

and

Barton F. Haynes

Duke University Arthritis Center

Division of Rheumatology, Allergy, and Immunology

Duke University Medical Center

## References

1. Picker, L.J., M.K. Singh, Z. Zdraveski, J.R. Treer, S.L. Waldrop, P.R. Bergstresser, and V.C. Maino. 1995. Direct demonstration of cytokine synthesis heterogeneity among human memory/effector T cells by flow cytometry. *Blood*. 86:1408–1419.
2. Kouskoff, V., A.S. Korganow, V. Duchatelle, C. Degott, C. Benoist, and D. Mathis. 1996. Organ-specific disease provoked by systemic autoimmunity. *Cell*. 87:811–822.
3. Pannetier, C., J. Even, and P. Kourilsky. 1995. T cell repertoire diversity and clonal expansions in normal and clinical samples. *Immunol. Today*. 16:176–181.
4. McHeyzer-Williams, M.G., J.D. Altman, and M.M. Davis. 1996. Enumeration and characterization of memory cells in the TH compartment. *Immunol. Rev.* 150:5–21.
5. McMichael, A.J., and C.A. O'Callaghan. 1998. A new look at T cells. *J. Exp. Med.* 187:1367–1371.
6. Gottlieb, P.A., and G.S. Eisenbarth. 1996. Mouse and man: multiple genes and multiple autoantigens in the aetiology of type I DM and related autoimmune disorders. *J. Autoimmun.* 9:277–281.
7. Winchester, R. 1994. The molecular basis of susceptibility to rheumatoid arthritis. *Adv. Immunol.* 56:389–466.
8. Estess, P., H.C. DeGrendele, V. Pascual, P. Estess, and M.H. Siegelman. 1998. Functional activation of lymphocyte CD44 in peripheral blood is a marker of autoimmune disease activity. *J. Clin. Invest.* 102:1173–1182.
9. Haynes, B.F., M.J. Telen, L.P. Hale, and S.M. Denning. 1989. CD44: a molecule involved in leukocyte adherence and T cell activation. *Immunol. Today*. 10:423–428.
10. Haynes, B.F., L.P. Hale, K.L. Patton, M.E. Martin, and R.M. McCalum. 1991. Measurement of an adhesion molecule as an indicator of inflammatory disease activity. Up-regulation of the receptor for hyaluronate (CD44) in rheumatoid arthritis. *Arthritis Rheum.* 34:1434–1443.
11. Mikecz, K., F.R. Brennan, J.H. Kim, and T.T. Glant. 1995. Anti-CD44 treatment abrogates tissue oedema and leukocyte infiltration in murine arthritis. *Nat. Med.* 1:558–563.
12. Levesque, M.C., and B.F. Haynes. 1997. Cytokine induction of the ability of human monocyte CD44 to bind hyaluronan is mediated primarily by TNF-alpha and is inhibited by IL-4 and IL-13. *J. Immunol.* 159:6184–6194.