Clinical and Experimental Rheumatology 2006; 24: 491-492.

Is B-cell the conductor of the lymphocyte orchestra in the salivary glands of patients with primary Sjögren's syndrome

P. Youinou, C. Daridon, A. Saraux, V. Devauchelle, J.-O. Pers

Laboratory of Immunology, Brest University Medical School Hospital, Brest, France.

Pierre Youinou, MD DSc; Capucine Daridon, BSc; Alain Saraux, MD PhD; Valérie Devauchelle, MD PhD; Jacques-Olivier Pers, DDS PhD.

Please address correspondence and reprint requests to: Dr. Pierre Youinou, Laboratory of Immunology, Brest University Medical School Hospital, BP 824, F29609 Brest Cedex, France.
E-mail: youinou@univ-brest.fr

Received on July 6, 2006; accepted on September 20, 2006.

Key words: Sjögren's syndrome, B-lymphocyte, cytokine.

Sjögren's syndrome (SS) is a chronic autoimmune epithelitis, of which the hallmarks are a disruption of epithelial cells, and the ensuing lymphoplasmocytic infiltration of exocrine tissue (1). This disorder may occur alone as primary SS, or set against a background of connective tissue disease as secondary SS.

It is not yet clear how glandular lesions are produced in SS, but many investigators have emphasized the predominance of lymphocytes demonstrable in the salivary glands (SGs) themselves (2). Furthermore, controversy still persists over which type of lymphocytes, B or T, initiates the process. On the basis that the SG infiltration in SS is composed mainly of $CD4^+$ T lymphocytes, T-cells may be viewed as competent in their own right, with B-cells confined to autoantibody production, and susceptibility to malignant clone escape. New evidence has, however, sparked off a great deal of interest in the possibility of B-cells playing a central role in the pathogenesis of SS (3). Such a possibility is all the more attractive that these lymphocytes represent around 15% of mononuclear cells included in the infiltrate (4).

Cytokines are thought to be instrumental in the promotion of cellular and humoral autoimmune processes, most notably those cytokines involved in T-helper (Th) type 1-driven responses. Transcripts for Th1-type cytokines, including interleukin (IL)-2, have thus been identified in the SGs of patients with primary SS (5), but transcripts for Th2-type cytokines including IL-4, have also been reported to be expressed (6). One explanation is that the Th1/Th2 cytokine balance changes with the progress of the immunopathological lesion of SS (7).

Beyond the paradigm that, at least with respect to T-cell-dependent responses, T-lymphocytes maintain strict control over B-lymphocytes, it is now acknowledged that the latter cells have the capacity to solicit their own help from the former (8), and thus to produce a flurry of autoAbs and cytokines (8). It is even more important that naïve B-cells differentiate themselves into polarized B-cells with different cytokine profiles, following stimulation with antigen and polarized effector Th1 and Th2. The newly polarized B-cells have been termed B effector (Be)1, making among others IL-2 and interferon (IFN)-γ, and Be2, making among others IL-4 and IL-6, respectively (9), inasmuch as, once induced, they regulate the level of Th1 and Th2 cells. Consequently, Be1 cells, by virtue of their production of IFN-γ and presentation of specific antigen to T-lymphocyte, promote the expansion of Th1 cells. In contrast, IL-4 produced by Be2 cells encourages the development of Th2 cells. Therefore, Be1 and Be2 cells behave as classical antigen-presenting cells that regulate the profile of the immune response.

As an attempt to sort it out in patients with primary SS (Fig. 1), tissue sections from their SGs were analyzed. Transcripts for IFN-γ, as a clue for the Th1 and Be1 nature of the cells, was detected by *in situ* hybridization using digoxigenin-labelled probe (GeneDetect, Auckland, New-Zealand) developed with fluorescein isothiocyanate-conjugated donkey anti-digoxigenin antibody. The lineage of these lymphocytes was identified using anti-CD3 or anti-CD19 monoclonal antibodies developed with tetramethyl rhodamine isothiocyanate-conjugated donkey anti-mouse antibody (Beckman Coulter, Hialeah, FL). Confocal microscopy examination revealed the presence of Th1 as well as Be1 cells. The Be1 phenotype may have been imprinted by Th1 cells, but this phenotype (which predominates over the Th2 phenotype at that site) may have been promoted by Be1 cells.

Thus, interest revives B-lymphocytes as contributors to the cause of SS (10). Although there is still a long way before setting up a unifying model for how such a B-cell hyperactivity leads to the disease, we are rather close to understand the way these cells process in autoimmune conditions. Intense efforts are ongoing for improved treatment. As a result, it has became likely that B-cell ablative treatments of SS should be completed in the next few months.

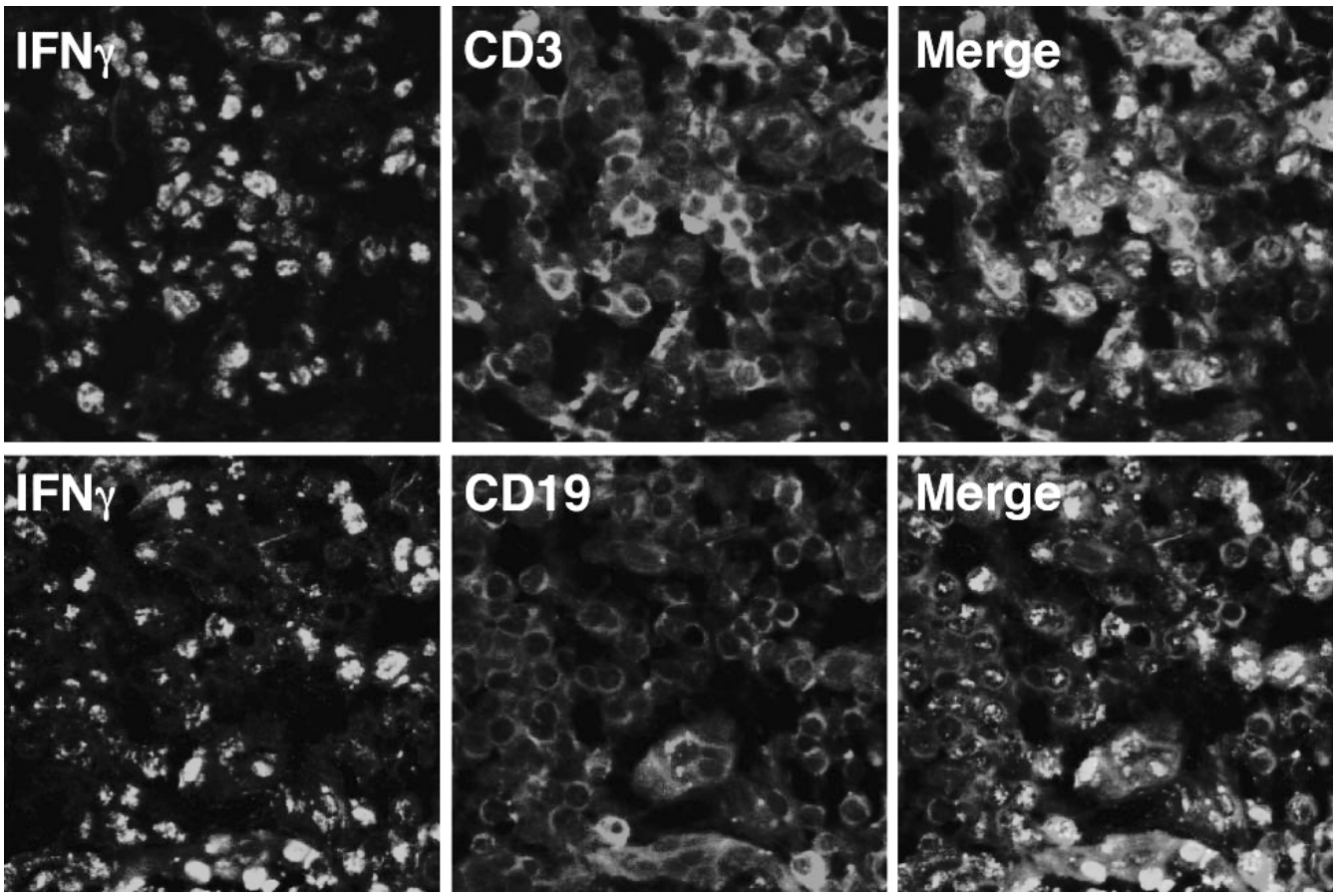

Fig. 1 : The transcripts for interferon-γ were visualized by *in situ* hybridization, plus fluorescein isothiocyanate-conjugated antibody (Ab), and the lymphocyte lineage identified with anti-CD3 (upper row) or anti-CD19 monoclonal Ab (lower row), plus tetramethyl rhodamine isothiocyanate-conjugated Ab.

References

1. MOUTSOPOULOS HM: Immunopathology of Sjögren's syndrome: more questions than answers. *Lupus* 1993; 2: 209-11.
2. JONSSON R, KRONELD U, BACKMAN K, MAGNUSSON B, TARKOWSKI A: Progression of sialadenitis in Sjögren's syndrome. *Br J Rheumatol* 1993; 32: 578-81.
3. HANSEN A, LIPSKY PE, DORNER T: Immunopathogenesis of primary Sjögren's syndrome: implications for disease management and therapy. *Curr Opin Rheumatol* 2005; 17: 558-65.
4. YOUINOU P, DARIDON C, STEINFELD S, PERS JO: A case for B-cells in the pathogenesis of Sjögren's syndrome. *Trends Immunol* (in press).
5. OHYAMA Y, NAKAMURA S, MATSUZAKI G *et al.*: Cytokine messenger RNA expression in the labial salivary glands of patients with Sjögren's syndrome. *Arthritis Rheum* 1996; 39: 1376-84.
6. BOUMBA D, SKOPOULI FN, MOUTSOPOULOS HM: Cytokine mRNA expression in the labial salivary gland tissues from patients with primary Sjögren's syndrome. *Br J Rheumatol* 1995; 34: 326-33.
7. MITSIAS DI, TZIOUFAS AG, VEIOPOULOU C *et al.*: The Th1/Th2 cytokine balance changes with the progress of the immunopathological lesion of Sjögren's syndrome. *Clin Exp Immunol* 2002; 128: 562-8.
8. STOCKINGER B, ZAL T, ZAL A, GRAY D: B cells solicit their own help from T cells. *J Exp Med* 1996; 183: 891-9.
9. HARRIS DP, HAYNES L, SAYLES PC *et al.*: Reciprocal regulation of polarized cytokine production by effector B and T cells. *Nat Immunol* 2000; 1: 475-82.
10. BROWNING JL: B cells move to centre stage: novel opportunities for autoimmune disease treatment. *Nat Rev Drug Discov* 2006; 5: 564-76.