Agents and Actions, vol. 19, 5/6 (1986)

0065-4299/86/060274-03 $ 1.50+0.20/0
© 1986 Birkhäuser Verlag, Basel

Decreased tissue immunoregulatory index in rheumatoid synovitis, determined by in-situ T-cell phenotyping with monoclonal antibodies

R. Dreher

Clinic for Rheumatic Diseases, Bad Kreuznach, BRD

In patients with rheumatoid arthritis T4-helper/inducer cells were found to be increased in peripheral blood [1–4], whereas in rheumatoid joint effusions T8-cytotoxic/suppressor cells were reported to be elevated [3, 5–7]. In cells eluted from rheumatoid synovial tissue an equal number of T4- and T8-cells or an enhanced number of T8-cells was demonstrated [6, 8–10]. In rheumatoid synovium tissue sections mainly increased numbers of the T4-cells subset are reported [11–13].
On the other hand there were few reports indicating a predominance of T8-cells in rheumatoid tissue [6, 14]. In an immuno-electron microscopic study [15] a positive correlation could be shown between the percentage of T4 staining cells and the total number of lymphocytes in a given area, whereas T8-staining cells correlated negatively. In contrast to the lymphocyte-rich tissue areas, the transitional areas, e.g. between lymphoid follicles showed low immunoregulatory indices (T4:T8 ratio = 0.8).
Thus the results on the immunoregulatory indices (T4:T8 ratio) in patients with rheumatoid arthritis appear contradictory and seem to be different, depending on the T-cell compartment (peripheral blood, joint effusion, synovial tissue) investigated.
In our studies rheumatoid tissue samples obtained by synovectomy were analysed immunohistologically using monoclonal antibodies for in situ T-cell phenotyping (OKT-series, monoclonals M522, T411, T811 from the Institute of Immunology, University Munich, Prof. Rieber).
Based on classical synovial membrane histology, we had special interest in the T-cell tissue distribution, depending on the rheumatoid synovitic reaction, such as ectopic lymphoid follicles, perivascular lymphoid aggregations in the sublining areas or diffuse lymphoid infiltrations boardering the hyperplastic lining cell layer.

Material and methods

Synovectomy tissue samples of 65 cases of rheumatoid arthritis and 44 cases of osteoarthritis were analysed as described elsewhere [16–19]. Local tissue immunoregulatory indices were calculated as the phenotypic T4:T8 ratios in a given tissue area on 4 μ step-wise native tissue sections.

Results

In given areas of the rheumatoid synovial membranes significant differences in the phenotypic immunoregulatory indices were determined. Within ectopic lymphoid follicles there is a clear T4-cell predominance (T4:T8 ratio = 2.2 ± 0.6), whereas within the perivascular T-cell infiltrates/aggregations (T4:T8 = 0.9 ± 0.3) and particularly within the diffuse infiltrations near the lining cell layer, the T8-cell subset population dominates (T4:T8 ratio = 0.3 ± 0.05), see Fig. 1. We were unable to confirm T4-lymphocyte/HLA-DR$^+$-macrophage cell contacts as described typically for the rheumatoid tissue lesion [11].

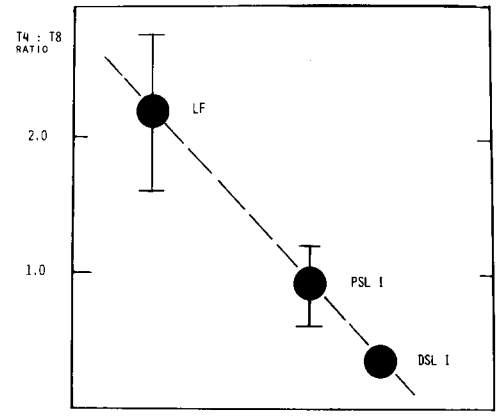

Figure 1
Decrease in the Tissue Phenotypic Immunoregulatory Index within the rheumatoid synovial membrane, depending on the lymphoid-infiltrated tissue area. LF = ectopic lymphoid follicle; PSLI = perivasal sublining infiltrations/aggregations; DSLI = diffuse sublining lymphoid infiltrations/aggregations.

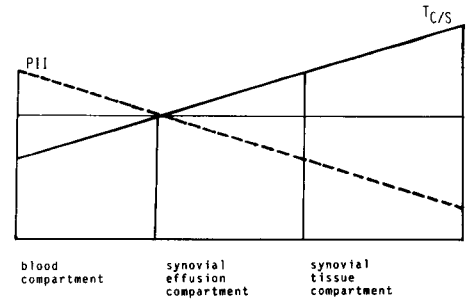

Figure 2
Decrease in the Phenotypic Immunoregulatory Index (PII) as a result of an increase in T8 cytotoxic/suppressive cells ($T_{c/s}$) depending on the lymphoid compartments as a pathogenetic principle in rheumatoid arthritis.

In osteoarthritic synovitis we found no ectopic lymphoid follicles. In perivascular areas in osteoarthritis synovitis (T4:T8 ratio = 1.5 ± 0.8) and rheumatoid synovitis (T4:T8 ratio = 0.9 ± 0.3) only quantitative differences were observed, whereas in the sublining area the qualitative differences appear to be significant (rheumatoid T4:T8 ratio = 0.3 ± 0.05 < osteoarthritic T4:T8 ratio = 0.6 ± 0.2).

Conclusion

The phenotypic tissue immunoregulatory index in rheumatoid synovitis is locally different and varies significantly between given areas. Ectopic lymphoid follicles show normal to high T4:T8 ratios, whereas within the sublining perivascular and diffuse infiltrate T4:T8 ratios are decreased. Thus the frequently reported immunoregulatory indices of eluted cells can't be representative for an immunoregulatory tissue disequilibrium in rheumatoid arthritis. An elevated T4:T8 ratio in eluted cells may correlate with a follicular B-cell hyperplasia in rheumatoid synovitis (low local activity), a low T4:T8 ratio may be related to rheumatoid synovitis with diffuse sublining T-cell infiltrates (high local activity). Our results are in principal accordance with the findings of Kurosaka and Ziff [15] and Meijer et al. [13]. They also found different T-cell distributions in synovial tissue depending on the histopathological localization.

For these topographical reasons, immunoregulatory indices determined in eluted cells from tissue samples cannot be representative for the immunopathological reactions at the synovial membrane tissue level.

The decrease in the phenotypic tissue immunoregulatory index in the rheumatoid synovium from deeper to superficial areas may be explained as a compensatory influx of peripheral, functionally defect T8-cytotoxic/suppressor cells (see Fig. 2).

References

[1] G. C. Faure, M. A. Bach, M. C. Bene, M. F. Kahn, H. A. Gaucher and J. F. Bach, *T-cell subsets in peripheral blood from rheumatoid arthritis people.* XV. Int. Congress of Rheumatology, Paris 1981, abstract 72.

[2] P. H. Hermans, E. M. Veys, G. Goldstein, P. Kung, J. Schindler, J. Symoens and J. van Wauwe, *Analysis of the T-cell populations determined by monoclonal antibodies in rheumatoid arthritis.* XV. Int. Congress of Rheumatology, Paris 1981, abstract 73.

[3] M. Duclos, H. Zeidler, Liman, W. L. Pichler, P. Rieber and H. H. Peter, *Characterization of blood and synovial fluid lymphocytes from patients with rheumatoid arthritis and other joint diseases by monoclonal antibodies (OKT series) and acid-alpha-naphtylesterase staining.* Rheumatol. Int. *2*, 75–82 (1982).

[4] F. Raeman, W. De Cock, F. Leempoels, J. De Cree and H. Verhaegen, *Enumeration of T-lymphocytes and T-lymphocyte subsets in rheumatoid arthritis using monoclonal antibodies.* Clin. Rheumatol. *1* (1981) (abstract).

[5] P. Lydyard, A. Hanglow, I. Hartley, A. Young and I. M. Roitt, *Immunoregulation in patients with rheumatoid arthritis.* Lancet *799* (1982).

[6] G. R. Burmeister, D. T. Y. Yu, A. M. Irani, H. G. Kunkel and R. J. Winchester, *Ia^+ T-cells in synovial fluid and tissues of patients with rheumatoid arthritis.* Arthritis Rheum. *24,* 1370–1376 (1981).

[7] E. M. Veys, P. Hermans, G. Verbruggen, J. Schindler and G. Goldstein, *Evaluation of T cell subsets with monoclonal antibodies in synovial fluid in rheumatoid arthritis.* J. Rheumatol. *9,* 821 (1982).

[8] A. Ranke, T. Paavonen, E. Tolvanen, Y. Konttinen, E. Kankaanpää, Nilson and G. Biberfeld, *Suppressor and helper T cells in rheumatoid synovia.* XV. Congress of Rheumatology, Paris 1981, abstract 70.

[9] J. G. Saal, H. Rautenstrauch, P. Fritz, W. Laschner and M. R. Hadam, *T-lymphocytes with Fc-receptors for IgG are highly enriched in synovium of rheumatoid arthritis.* XV. Congress of Rheumatology, Paris 1981, abstract 71.

[10] T. Egeland and O. Forre, *Eluted rheumatoid synovial tissue T cell subsets and HLA-DR bearing cells at different stages of fractionation.* Clinical Rheumatology *2,* 1, 19–26 (1983).

[11] G. Janossy, O. Duke, L. W. Poulter, G. Panayi, M. Bofill and G. Goldstein, *Rheumatoid arthritis: a disease of T-lymphocyte/macrophage immunoregulation.* Lancet *17,* 839–842 (1981).

[12] L. Klareskog, U. Forsum, M. Tjernlund, D. Kabelitz and A. Wigren, *Appearance of anti HLA-DR-reactive cells in normal and rheumatoid synovial tissue.* Scand. J. Immunol. *14,* 183–192 (1981).

[13] C. J. L. M. Meijer, C. B. de Graaff-Reitsman, G. J. M. Lafebar and A. Cats, *In situ localization of lymphocyte subsets in synovial membranes of patients with rheumatoid arthritis with monoclonal antibodies.* J. Rheumatol. *9,* 359–365 (1982).

[14] R. I. Fox, T. C. Adamson, D. Frisman, I. Royston and J. H. Vaughan, *Identification of lymphocytes infiltrating synovial membrane in rheumatoid arthritis.* Arthritis Rheum. *25,* 50 (1982) (abstract).

[15] M. Kurosaka and M. Ziff, *Immunelectron microscopy study of the distribution of T cell subsets in rheumatoid synovium.* J. Exp. Med. *158,* 1191–1210 (1983).

[16] R. Dreher, C. H. Görner, U. Macholt, B. Rohrbach and K. Federlin, *Klassifikation der synovitischen Reaktionstypen bei rheumatoider Arthritis aufgrund zellkinetisch-morphologischer Befunde bei der experimentellen Immunarthritis.* Immun. Infekt. *9,* 204–212 (1981).

[17] R. Dreher and K. Federlin, *Die Bedeutung der funktionellen Morphologie, Immunregulation und -hämostasiologie für die Klinik der rheumatoiden Arthritis.* 88. Tagung Dtsch. Ges. Innere Med. Wiesbaden, April 1982.

[18] R. Dreher, U. Weber, B. Rohrbach, G. Köhler, W. Mohing and K. Federlin, *Histologische Synoviaanalyse mit monoklonalen Antikörpern.* Zschr. Rheumatologie *41,* 4, 120–121 (1982).

[19] R. Dreher, *Experimentelle Immunarthritis und ihre Bedeutung in der Rheumatherapieforschung und Rheumapathologie.* Werksverlag Dr. E. Banaschewski, München-Gräfelfing 1983.