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GENERAL MECHANISMS OF INFLAMMATION IN RHEUMATOID ARTHRITIS

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Summary

Rheumatoid synovitis is characterized by the simultaneous occurrence of two major types of immunologically-induced inflammation. These usually occur concurrently in the same joint. A cellular immune response is present in the sublining layer of the synovial membrane and an immune complex-induced acute inflammatory reaction is present in the synovial effusion phase of the disease. The two reactions are closely related and mutually interdependent. The cellular immune response is reduced in rheumatoid arthritis, but the chronic inflammatory cells of the synovium are active in the synthesis of IgG and probably considerable amounts of IgG rheumatoid factor. Rheumatoid factor complexes, particularly IgG-RF complexes, appear to be responsible for the exudative, immune complex-induced inflammatory phase of the disease.

Zusammenfassung

Die rheumatoide Synovitis ist durch das gleichzeitige Auftreten von zwei Typen von immunologisch bedingter Entzündung charakterisiert. Beide Typen kommen in der Regel zusammen im gleichen Gelenk vor. Eine zelluläre Immunantwort findet im Gewebe unter der Synovialmembran statt und eine akute entzündliche Reaktion, die durch Immunkomplexe ausgelöst wird, spielt sich in der exsudativen Phase der Krankheit ab. Die zwei Reaktionen sind voneinander gegenseitig abhängig. Die zelluläre Immunantwort ist in der rheumatoiden Arthritis herabgesetzt, aber die Entzündungszellen der chronischen Synovitis synthetisieren aktiv Immunglobuline und wahrscheinlich auch erhebliche Mengen von IgG-Rheumafaktor. Rheumafaktor-Komplexe, speziell IgG-RF-Komplexe, scheinen für die exsudative Immunkomplex-bedingte entzündliche Phase der Krankheit verantwortlich zu sein.

Table I. Peripheral blood lymphocytes.

	Normals		RA	
	% E-RFC (T)	% S-Ig$^+$ (B)	% E-RFC (T)	% S-Ig$^+$ (B)
Utsinger and Bluestein, 1974	64	25	57	25
Brenner et al, 1974	66	16	68	12
Burmester et al, 1978	68	7	56	9

Table II. Lymphocyte populations in blood and synovial fluid of RA patients.

	Blood		Synovial Fluid	
	% E-RFC (T)	% S-Ig$^+$ (B)	% E-RFC (T)	% S-Ig$^+$ (B)
Sheldon et al, 1974	69	18	79	8
Brenner et al, 1975	69	17	76	15
Wangel and Klockars, 1977	64	27	57	19
Van de Putte et al, 1976	66	11	82	2
Utsinger, 1975	61	24	61	23

Rheumatoid synovitis is characterized by the simultaneous occurrence of two major types of immunologically induced inflammation which take place concurrently in the same joint. A cellular immune response is present in the sublining layer of the synovial membrane and an immune complex-induced acute inflammatory reaction is observed in the synovial effusion in which large numbers of polymorphonuclear cells (PMN) are present. The two reactions are closely interrelated.

Cellular Immune Response. Cellular immunity is reduced in rheumatoid arthritis (RA). There is diminished skin test reactivity (1), reduced capacity to acquire sensitization to dinitrochlorobenzene (2), and decreased responsiveness to mitogens (3). It has also been observed (4) that cellmediated immunity tends to decrease with duration of disease. These abnormalities have been observed to improve after treatment with gold salts or penicillamine. The pokeweed mitogen response, which involves a B cell as well as T cell response, is not depressed (5, 6). The decrease in cellular immunity is not due to a decrease in the numbers of circulating T lymphocytes (Table I) if one compares the per cent of E-rosette forming cells in the peripheral blood in RA patients and normals (7). Nor is there a decrease in the per cent of T lymphocytes in the RA synovial effusion as compared with the blood (Table II) (7-11).

There is no clear explanation for the decrease in cellular immunity in RA. This abnormality is not limited to rheumatoid arthritis, but is characteristic of a number of disease states associated with chronic inflammation. Three possibilities come to mind: 1. a lymphocytotoxic antibody directed at the T cell may be responsible for the diminished T cell function;

Table III. Lymphocytes in RA synovial tissue digests.

	% E-RFC (T)	% S-Ig$^+$ (B)
Bankhurst et al, 1976	78, 85	10, 17
Van Boxel and Paget, 1975	78	9-35
Abrahamsen et al, 1976	74	10

2. there may be an actual decrease in a mitogen responsive T cell population which is not reflected in total T cell counts; and 3. there may be an increase in the suppressor cell content of the circulating mononuclear cells. GOODWIN et al (12) have recently described a prostaglandin E producing macrophage in Hodgkins' disease which has a suppressive action on mitogen responsiveness.

Cellular Interactions in the Sublining Layer. The sublining layer of the RA synovium is the site of a chronic mononuclear inflammatory reaction; and also the site of extensive immunoglobulin (Ig) synthesis.

In lymphocyte cultures in which T lymphocytes undergo blastic transformation, lymphokines are produced. Lymphokines are mediators of the cellular immune response, and when detected indicate that T lymphocyte transformation has taken place in the culture. When rheumatoid synovial effusions were examined for the presence of macrophage migration inhibitory factor (MIF) and mitogenic factor, these lymphokines were detected in RA synovial effusions, providing evidence for the occurrence of blastic transformation of T lymphocytes in this tissue (13). Some insight into the cellular events in the RA synovial membrane is provided by electron microscopic evidence. In the sublining layer, there is an emigration of small lymphocytes from the post-capillary venule (14) producing perivenular collections consisting almost entirely of small lymphocytes. It may be supposed that these cells, presumably a mixture of T and B cells, leave the blood in the ratio in which they circulate in the blood. A number of studies have provided evidence that this may be so. By fluorescent antibody staining of the synovial tissue with anti-theta serum (15) and by fluorescent antibody staining of cells obtained by digestion of synovial tissue pieces with collagenase (16, 17), it has been found that between 74 and 85 per cent of the synovial tissue lymphocytes are T lymphocytes (Table III). This is close to the percentage of these cells which is found in the blood.

Near the perivenular small lymphocyte collections, one finds transitional zones of mononuclear cells. These are rich in large blastic cells which have the appearance of T lymphoblasts. Some plasma cells are present, and large numbers of macrophages appear to have been attracted into these areas perhaps as a result of the elaboration of MIF from the blastic cells.

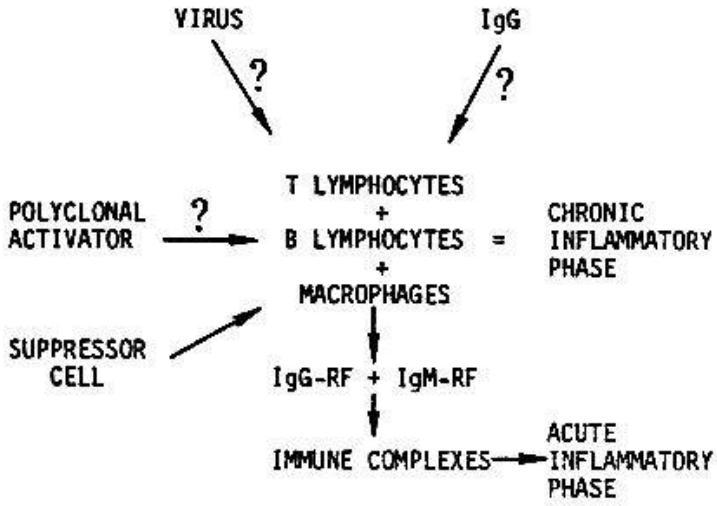

Fig. 1. Cellular and humoral responses of the rheumatoid synovial membrane.

One must presume that the small lymphocytes which have emigrated from the post-capillary venules have undergone transformation as a result of stimulation by a local agent, be it antigen or mitogen, or in the case of B cells, a polyclonal activator.

In the most mature cellular infiltrates, there are frequent perivascular cell collections which consist mainly of plasma cells. These are actively synthesizing IgG as discussed below.

Immunoglobulin Synthesis. The synovial membrane produces large amounts of Ig as has been shown (18) by measuring the incorporation of C14 amino acids into the Ig produced by synovial tissue pieces in culture. Most of the Ig synthesized by the RA synovium was IgG. The amount synthesized was observed to be greater than that produced by normal human lymphoid tissue and similar to that produced by normal human spleen. It has been calculated by ZVAIFLER (19) that 12 to 24 per cent of the IgG in RA synovial fluid is derived from local production. No evidence of local synthesis was observed in the joints of patients with Reiter's syndrome or degenerative joint disease.

What is the nature of the IgG that the RA synovial membrane synthesizes? By fluorescent antibody staining of RA synovial tissue, MUNTHE and NATVIG (20) found that plasma cells containing IgG were dominant in all membranes examined whether obtained from seropositive or seronegative patients. Following pepsin digestion to reveal "hidden rheumatoid factor activity", these workers observed a remarkable increase in the ability of the tissues to bind IgG. Following such treatment, 50 to 75 per cent of the plasma cells in the synovial tissue of seropositive patients bound aggregated IgG indicating that they were synthesizing rheumatoid factor (RF). It appears from this work that the major protein synthesized by RA synovial tissue is IgG-RF. Recently, evidence has been presented (21) that IgG-RF reacts with itself to form self-associated IgG-RF complexes. The demonstration of the synthesis of

relative large quantities of IgG-RF in the synovial membrane is consistent with the important role which self-associated RF complexes appear to play in the synovial effusion phase of rheumatoid synovitis as will be discussed below.

Immune Complex Phase of Rheumatoid Synovitis. Complement levels are generally decreased in RA synovial effusions (22-24). WINCHESTER, AGNELLO and KUNKEL (25) have shown that it is the self-associated IgG-RF complex in the synovial fluid which is mainly responsible for the reduced complement levels in rheumatoid effusions. The activation of complement by synovial fluid complexes leads to the formation of a chemotactic C5, C6, C7 complex and a chemotactic C5a component which attract PMN into the fluid. This explains the relatively high concentration of polymorphonuclear cells which is present in most rheumatoid fluids.

Phagocytosis of Synovial Fluid Complexes. IgG-RF may combine with IgM-RF and complement to form (IgG-RF)n-IgM-RF-C' complexes. These complexes may be phagocytosed by the phagocytic lining cells of the synovium and by the polymorphonuclear cells in the synovial fluid with the formation of inclusions. The phagocytosis of these inclusions may lead to further inflammation by bringing about the release of lysosomal enzymes from the phagocytic cells. KINSELLA, BAUM and ZIFF (26) have shown that the phagocytic type A cells, digested from rheumatoid synovial tissue by trypsin, contain intracellular inclusions. These stained positively for IgG, IgM and the complement components C1q and C3. HURD, LOSPALLUTO and ZIFF (27) obtained similar results upon incubation of rheumatoid synovial fluid with normal PMN indicating that similar immune complexes are also taken up by PMN. Release of lysosomal enzymes has been shown to occur (28) following uptake of aggregated IgG by PMN. Lysosomal protease may activate C5 to C5a which has anaphylotoxic and chemotactic properties. C5a is also effective in stimulating the release of lysosomal enzymes from PMN (29). These reactions provide a clear basis for the acute inflammatory phase of rheumatoid synovitis. It is noteworthy that the immune complexes involved are rheumatoid factor complexes and that IgG-RF, produced in the synovial tissue, plays a central role in the formation of these complexes.

Initiation of the Rheumatoid Synovial Response. The source of stimulation of the immune response occurring in the RA synovium is not known. Speculation has centered around two possibilities: 1. an infectious agent, and 2. IgG acting as an autoantigen. No convincing evidence for an infectious etiology is at present available. Investigations of the antigenic activity of IgG in rheumatoid arthritis have been conflicting. A number of reports (30-32) have failed to observe blastic transformation of circulating rheumatoid lymphocytes upon incubation with IgG. On the other hand, KINSELLA (33) found that aggregated IgG produced significant transformation of the majority of samples of circulating lymphocytes from RA pa-

tients. The response required the presence of complement. Similar results, however, were obtained with the lymphocytes of patients with ankylosing spondylitis. FRØLAND and GAARDER (34) and CLOT et al (35) observed that heat-aggregated human IgG caused migration inhibition of buffy coat leukocytes of patients with RA. SANY et al (36) observed the production of leukocyte inhibitory factor (LIF) upon incubation of rheumatoid lymphocytes with aggregated IgG. Finally, YAMASAKI and ZIFF (37) have observed enhancement of in vitro synthesis of Ig by rheumatoid lymphocytes when cultured with aggregated IgG.
It would appear from the above results that IgG is capable of stimulating rheumatoid lymphocytes to respond with blastic transformation, the elaboration of lymphokine, and even the synthesis of Ig. The mechanism of this response is not clear. It is possible that IgG is serving as a specific antigen, but it is also possible that a nonspecific effect is involved.

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