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Complement in acute and chronic arthritides: assessment of C3c, C9, and protectin (CD59) in synovial membrane

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Abstract

***Objectives*—To investigate the role of complement cascade induced damage and protection against it in acute arthritides compared to rheumatoid arthritis and other chronic joint derangements.**

***Methods*—C3c, C9, and protectin (CD59) were examined by avidin-biotin-peroxidase complex staining.**

***Results*—Marked deposits of C3c and C9 were found in synovial vasculature and intercellular matrix of the lining in rheumatoid arthritis and in acute arthritides (including bacterial, reactive, and osteoarthritis flare up). Furthermore, protectin was not visible in synovial lining cells and was relatively weakly expressed in stromal and endothelial cells in rheumatoid arthritis; also in acute arthritides protectin expression was weak. In contrast, C3c and C9 deposits were not found in chronic conditions associated with degenerative diseases (osteoarthritis and osteochondritis dissecans) or mechanical causes (patellar luxation and a ruptured meniscus), in which also the protectin expression was prominent in synovial lining, endothelial and some stromal cells.**

***Conclusions*—Activation of the complement in rheumatoid arthritis and in acute arthritides seems to be associated with a decreased protection of synovial cells against cellular effects and lysis mediated by membrane attack complex.**

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The complement system is involved in the host defence by recognition and elimination of potentially harmful exogenous and endogenous structures from the human body. Activation of complement may also promote inflammatory reactions and cause tissue damage if adequate control is not provided by the complement regulatory proteins.[1]

Significant amounts of biologically active products arising from complement activation have been detected in joint fluid[2–7] and tissues[8–10] under pathological conditions. It is thought, therefore, that protection of the host cells against complement mediated damage may be an important aspect relevant to the pathogenesis of both joint inflammation/injury and healing/removal of the altered structures. This is exemplified by the role of immune complexes and rheumatoid factors, which are established activators of the complement in rheumatoid arthritis.[11] Products of the activation of the early complement pathway, such as opsonins and anaphylatoxins, could in turn contribute to the clearance of immune complexes and other tissue debris, but could also promote local inflammatory reactions, for example through induction of neutrophils and mast cells.[12] Yet local activation of the late complement pathway (C5-C9) gives rise to the highly chemotactic C5a and leads to the formation of terminal complement complex (TCC).[7 13] Membrane attack complex (MAC), a lytic, cell membrane associated form of TCC, was shown to induce non-lethal stimulatory effects in synovial cells, for example by inducing them to produce reactive oxygen species and metabolites of arachidonic acid and interleukin-6, and by increasing the levels of collagenase specific messenger RNA (mRNA).[14–16] Similar non-lytic activities of MAC can be exerted on circulating cells, such as monocytes, neutrophils, and platelets. In addition, MAC can induce endothelial cells to release or mobilise the adhesive molecules, such as von Willebrand factor and GMP-140 (P-selectin).[17]

Assembly of MAC is inhibited in the fluid phase by vitronectin (protein S) and clusterin.[1] On the cell membrane, MAC is inhibited by the cell membrane associated inhibitors, such as homologous restriction factor (HRF) and protectin (CD59, HRF20, MIRL).[18] Høgåsen and colleagues have recently reported relatively low levels of vitronectin and clusterin in synovial fluid in rheumatoid arthritis, and concluded that this might allow lytic or sublytic attacks on local cells.[7] This suggests that above mentioned non-lytic effects of MAC might contribute to the perpetuation of inflammation and joint destruction in rheumatoid arthritis. Another relevant issue, which has received little attention, is the involvement of the complement system in acute-transient inflammatory reactions in joints, characterised by effusion and influx of inflammatory cells. Such reactions are seen in many different types of acute arthritis, including reactive, bacterial, flare up of chronic diseases, and acute mechanical joint derangements.

Our study was designed to extend observations on complement involvement and protection against it in synovial tissue in various arthritides. For this purpose, synovial

*Table 1 Characteristics of patients with acute arthritides**

Case No	Sex F/M	Age (years)	Type of acute arthritis/underlying condition	Joint	Duration of acute arthritis (days)	Possible aetiology	Synovial fluid: Gram stain	Synovial fluid: Culture	Blood culture	ANTB
1	M	49	Bacterial	Knee	14	Abscess of the thigh	POS	Staphylococcus aureus	POS	NO
2	M	24	Bacterial	Ankle	3	Unknown	NEG	Staphylococcus hominis	ND	NO
3	M	29	Bacterial	Knee	1	Haematogenous	NEG	Haemophilus influenza	NEG	NO
4	F	81	Bacterial/2 years unidentified polyarthritis	Wrist	14	Unknown	POS	Staphylococcus aureus	ND	NO
5	M	73	Bacterial/20 years RA	Knee	2	Unknown	NEG	Group A and B haemolytic streptococcus	ND	YES
6	M	28	Bacterial	Knee	1	Post-synovectomy	NEG	Staphylococcus aureus	NEG	NO
7	F	63	Bacterial	Knee	42	Intra-articular steroids 1 week before onset	NEG	Staphylococcus aureus	NEG	YES
8	M	20	Reactive	Knee	2	Yersinia enterocolitica IgM+++, IgG+++, IgA+++	NEG	NEG	NEG	NO
9	F	55	Reactive	Knee	5	Salmonella IgG+	NEG	NEG	NEG	YES
10	M	27	Suspected reactive**	Knee	2	Unknown**	NEG	NEG	NEG	NO
11	F	19	Suspected reactive**	Knee	4	Unknown**	NEG	NEG	NEG	NO
12	M	78	Flare up of OA	Knee	3	Unknown	NEG	NEG	NEG	NO
13	F	83	Flare up of OA	Knee	6	Unknown	NEG	NEG	NEG	NO
14	F	82	Flare up of OA	Knee	2	Unknown	NEG	NEG	NEG	YES
15	F	75	Flare up of OA	Knee	2	Unknown	NEG	NEG	NEG	NO
16	M	34	Traumatic with fracture of patella/10 years AS	Knee	3	Fracture of patella	NEG	NEG	NEG	YES
17	M	24	Traumatic with rupture of meniscus	Knee	4	Rupture of meniscus	ND	ND	ND	NO

* Abbreviations: M, male; F, female; RA, rheumatoid arthritis; OA, osteoarthritis; AS, ankylosing spondylitis; NEG, negative; POS, positive; ND, not done; ANTB, antibiotics during a period of two weeks.
** Suspected reactive arthritis with serologic tests negative for salmonella, yersinia, chlamydia, viral antibodies, shigella campylo, AST, ASTA, teichoic acid, and recovery in follow up.

samples collected from various arthritic conditions have been classified into: (1) acute arthritides, or (2) rheumatoid arthritis and other chronic joint derangements. Expression of protectin, the main cell membrane bound inhibitor of MAC, was studied in parallel with C3c and C9 to assess complement turnover, using a sensitive immunohistochemical technique.

Methods

PATIENTS AND SPECIMENS

With their informed consent, a synovial tissue specimen was obtained from each of 34 patients at joint arthrotomies or diagnostic/therapeutic arthroscopies. Of the specimens, 27 were samples from the knee, two from the wrist, one from the proximal interphalangeal joint, three from the ankle, and one from the elbow joint.

Clinical characteristics of patients with a flare up of arthritis (mean duration 6.5 days, range from one to 42 days)—an example of acute arthritis[19]—are presented in table 1. These were 10 males and 7 females, mean age 49.6 years, range from 19 to 83. The series comprised bacterial arthritis (n = 7; among them one with an underlying HLA-B27 positive, seronegative polyarthritis and one with underlying rheumatoid arthritis[20]), reactive arthritis (n = 4; three cases with positive HLA-B27 and two cases with negative serological tests), and traumatic arthritis (n = 2; one with an underlying ankylosing spondylitis), as well as four flare ups of osteoarthritis.[21]

Characteristics of the patients with rheumatoid arthritis and other chronic joint derangements of more than three months' duration are presented in table 2. These series included five patients (four females, one male, mean age 48.6 years, range from 33 to 63) with rheumatoid arthritis,[20] seven patients (two males and five females, mean age 68.6 years, range from 48 to 90) with osteoarthritis,[21] and two with traumatic injury of the knee joint (one case with patellar luxation and one with a ruptured meniscus). In addition, one case with osteochondritis dissecans, one with monoarticular destructive synovitis, and one with chronic monosynovitis (synovial fluid and blood cultures were negative) were included.

*Table 2 Characteristics of patients with rheumatoid arthritis and other joint derangements**

Case No	Sex	Age (years)	Diagnosis	Biopsy site	Disease duration (years)
1	F	63	RA	Wrist	5
2	F	54	RA	Ankle	35
3	F	48	RA	PIP	6
4	F	33	RA	Knee	20
5	M	45	RA	Ankle	18
6	M	79	OA	Knee	10
7	F	48	OA	Knee	5
8	F	72	OA	Knee	10
9	F	67	OA	Knee	13
10	M	62	OA	Knee	5
11	F	62	OA	Knee	20
12	F	90	OA	Knee	5
13	M	33	Rupture of meniscus	Knee	4/12
14	F	54	Luxation of patella	Knee	4/12
15	M	21	Osteochondritis dissecans	Knee	5
16	F	69	Monoarticular destructive synovitis	Elbow	1.5
17	M	37	Chronic monosynovitis	Knee	6/12

* Abbreviations: M, male; F, female; RA, rheumatoid arthritis; OA, osteoarthritis; PIP, proximal interphalangeal joint.

IMMUNOSTAINING OF C3c, C9, AND PROTECTIN

Snap frozen synovial samples were embedded in Tissue-Tek OCT compound (Lab-Tek Products, Elkhart, IN, USA) and stored at −20°C. Cryostat-cut sections (6 μm thick) from these specimens were applied to gelatin-formalin coated slides and fixed in cold acetone for five minutes. Endogenous peroxidase activity in the sections was inhibited with 0.3% H_2O_2 in methanol for 30 minutes. Immunostainings were performed using—where appropriate — a rabbit, goat, or mouse

*Table 3 Deposition of the complement components C3c, C9, and expression of the cell-associated complement inhibitor protectin (CD59) in synovial membranes in acute arthritides compared to rheumatoid arthritis and other chronic joint derangements**

Case No	Type of arthritis/underlying condition	C3c			C9			Protectin (CD59)		
		Synovial intima	Synovial stroma	Synovial vasculature	Synovial intima	Synovial stroma	Synovial vasculature	Synovial intimal cells	Synovial stromal cells	Synovial vasculature/ endothelium
Acute arthritides										
1	Bacterial	+	+	+	++	0	++	+/++	+/++	+/++
2	Bacterial	+	0	+	++	0	++	+/++	+/++	+/++
3	Bacterial	+	0	+	+	0	+	+/++	+	+
4	Bacterial/unidentified polyarthritis	0	+	+	0	0	+	++	++/+++	++/+++
5	Bacterial/RA	0	0	+	+	0	++	0	++	++
6	Bacterial	++	0	+	++	0	++	+/++	+/++	+/++
7	Bacterial	++	+	+	+++	0	++	+/++	+/++	+/++
8	Reactive	+	+	++	+	0	++	+/++	+/++	+/++
9	Reactive	++	+	+	+++	0	++	+/++	+/++	+/++
10	Suspected reactive	+	+	++	++	0	+++	+/++	+/++	++/+++
11	Suspected reactive	+	+	+	+	0	+	++/+++	++/+++	++
12	Flare up of OA	++	+	++	++	0	++	+/++	+/++	+/++
13	Flare up of OA	++	+	++	+++	0	++	+/++	+/++	+/++
14	Flare up of OA	++	+	++	+++	0	++	+/++	+/++	+/++
15	Flare up of OA	+	0	++	++	0	++	+/++	+/++	+/++
16	Traumatic with fracture of patella/AS	+	0	+	++	0	++	++	++	++
17	Traumatic with fracture of meniscus	0	0	+	0	0	+	++	++	++/+++
RA and other chronic joint derangements										
1	RA	++	0	0	++	0	+	0	+/++	+/++
2	RA	***	0	+	***	0	+++	***	+/++	+/++
3	RA	+	0	0	++	0	++	0	+/++	+/++
4	RA	+	0	0	++	0	++	0	+	+/++
5	RA	+	0	+	+	0	+	0	+/++	+/++
6	OA	0	+	+	0	0	+	++/+++	++/+++	+++
7	OA†	0	0	0	0	0	0	+++	+++	+++
8	OA†	0	0	+	+	0	+	++/+++	++/+++	+++
9	OA†	0	0	0	0	0	0	+++	++/+++	+++
10	OA†	0	0	+	+	0	+	++/+++	++/+++	+++
11	OA†	0	0	0	+	0	+	++/+++	++/+++	++/+++
12	OA	0	0	0	0	0	+	++/+++	++/+++	++/+++
13	Rupture of meniscus	0	0	+	0	0	+	+++	++/+++	++/+++
14	Luxation of patella	0	0	+	0	0	+	++++	++/+++	++
15	Osteochondritis dissecans	0	0	0	0	0	0	++/+++	++/+++	+++
16	Monoarticular destructive synovitis†	+	0	0	+	0	+	++	++	++
17	Chronic monosynovitis	0	0	0	0	0	0	++	++	++

* For clinical details refer to the corresponding case number in Tables 1 and 2, respectively.
Abbreviations: RA, rheumatoid arthritis; OA, osteoarthritis; AS, ankylosing spondylitis.
† In these cases, occasional perivascular infiltration with inflammatory cells was seen; *** Structure not identified.
Evaluation of the C3c and C9 staining/deposition - 0, deposits not found; +, deposits found occasionally; ++, scattered deposits; +++, extensive deposition.
Evaluation of the protectin (CD59) staining - 0, staining not detected; +, weak staining; ++, moderate staining; +++, strong staining.

Vectastain *Elite* ABC kit (Vector Laboratories, Burlingame, CA, USA). Briefly, consecutive synovial sections were incubated in: (1) normal serum (dilution 1:60); (2) primary antibody: rabbit anti-human C3c (1:130; Behringwerke AG, Marburgh, Germany) or goat anti-human C9 (1:100; Quidel Corporation, San Diego, CA, USA), or monoclonal mouse anti-human CD59 (1:200; BRIC, Bio-Products Laboratory, Elstree, UK) for 60 minutes; (3) secondary/biotinylated antibody (1:133); (4) avidin-biotin-peroxidase complex (1:100) for 30 minutes; (5) 3,3'-diaminobenzidine tetrahydrochloride (Sigma, St Louis, MO, USA) in 0.006% H_2O_2 solution in tris buffered saline (TBS; 0.05 M tris[hydroxymethyl]aminomethane, 0.15 M saline, pH 7.4). Consecutive sections were counterstained with Harris haematoxylin or left without counterstain, dehydrated, cleared in xylol, and mounted in Diatex (Becker Industrifärg, Märsta, Sweden).

A 0.1% solution of bovine serum albumin in TBS was used for dilution of the primary antibodies and sera. Between steps of the staining the slides were washed in TBS. Omission of the primary antibody and exposure of tissue sections to DAB/hydrogen peroxide (for endogenous peroxidase) were used as a negative staining control.

Results

Results of the immunostaining for C3c, C9, and CD59 are presented in table 3. In summary, positive immunostaining for C3c (if any) was only occasionally observed in the basement membrane of blood vessels in synovial samples from chronic joint derangements due to degenerative diseases and mechanical causes (fig 1A). In rheumatoid arthritis and acute arthritides, C3c staining/deposits (granular pattern mixed with diffuse staining) were observed occasionally or scattered in the synovial lining, vasculature, and in the deeper synovium (fig 1B and C); in some cases in a close proximity to the synovial lining and stromal cells. The cases No 4 and No 5 (table 1) with infectious arthritis superimposed on an underlying chronic arthritis did not disclose C3c deposition (not shown).

Immunostaining for C9 in the synovial membranes showed a granular pattern and was

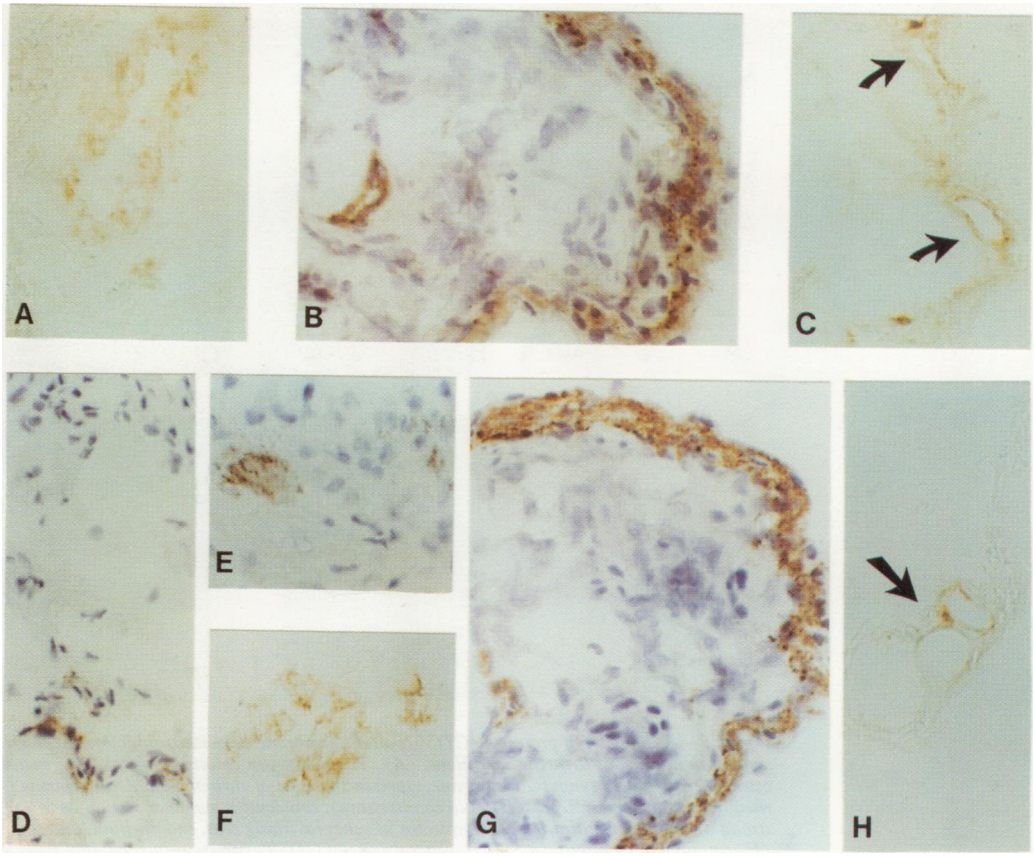

Figure 1 Immunostaining of C3c (the split product of the early complement cascade) (panels A-C) and C9 (panels D-H) in synovial membranes in various arthritic conditions. (A) (No counterstain): synovial membrane from osteoarthritis (OA) represents a set of chronic joint derangements (see table 2, exclude cases with rheumatoid arthritis (RA)); note the staining of C3c in the basement membrane of a large blood vessel; this was only occasionally visible in chronic joint derangements. In contrast, comparatively marked C3c staining was visible in synovial lining and vasculature in acute arthritides. (B) (Haematoxylin counterstain): synovium from flare-up of OA. (C) (No counterstain): synovium with acute reactive arthritis (staining of C3c in blood vessels in this case is indicated by arrows). (D) (No counterstain): synovial membrane from joint with OA represents a set of chronic joint derangements (see table 2, exclude cases with RA); in this case, note staining of C9 in synovial vasculature; this was only occasionally visible in chronic joint derangements. In contrast, marked extracellular deposits of C9 were visible in synovial intimal layer and vasculature in RA and acute arthritides. (E) (Haematoxylin counterstain). (F) (No counterstain): consecutive synovial sections from RA specimen. (G) (Haematoxylin counterstain): synovium from flare up of OA. (H) (No counterstain): synovium from acute reactive arthritis (staining of C9 in blood vessels in this case is indicated by arrow). (ABC technique, frozen synovial tissue sections, ×325).

mainly associated with the synovial intima and vasculature, but was not found in the cytoplasm of lining and endothelial cells. However, C9 staining differed in the acute and rheumatoid arthritis from that in other forms of chronic joint derangements. Synovial membranes from the latter conditions caused by degenerative diseases (osteoarthritis, osteochondritis) or mechanical causes (luxation of patella, meniscus lesion) showed only negligible C9 deposition (fig 1D). In contrast, three out of five synovial samples from rheumatoid arthritis, and synovial membranes from acute arthritides, showed scattered or extensive C9 deposits in the extracellular matrix of synovial intima and in vasculature (fig 1E to H). Two cases with acute bacterial arthritis superimposed on an underlying polyarthritis (cases No 4 and No 5, table 1) lacked substantial C9 deposition, though some C9 was detected in the vasculature (not shown).

Although the present series included synovial samples from patients with different durations of acute arthritis, their number was too low to allow detection of eventual relations between duration of arthritis and deposition of the complement components studied.

Expression of the complement MAC inhibitor protectin was observed in the synovial lining, some stromal cells, and vasculature. In contrast to the extracellular C9 and C3c, staining of the protectin was associated with the cytoplasm of these cells. An inverse relation was detected between C9 deposition and protectin expression: in all synovial membranes with chronic joint derangements due to degenerative diseases or mechanical causes (specified above), vascular endothelium and synovial lining disclosed moderate to strong protectin immunoreactivity (fig 2, A and B). In acute arthritides and in endothelial cells in rheumatoid arthritis, expression of the protectin was weaker (fig 2, C-F). Furthermore, protectin could not be found in synovial cells in rheumatoid arthritis samples showing extensive synovial hyperplasia (fig 2, C and D).

Discussion

Activation of the complement system has been established in the pathological joint fluid and tissues, indicating that complement may be an

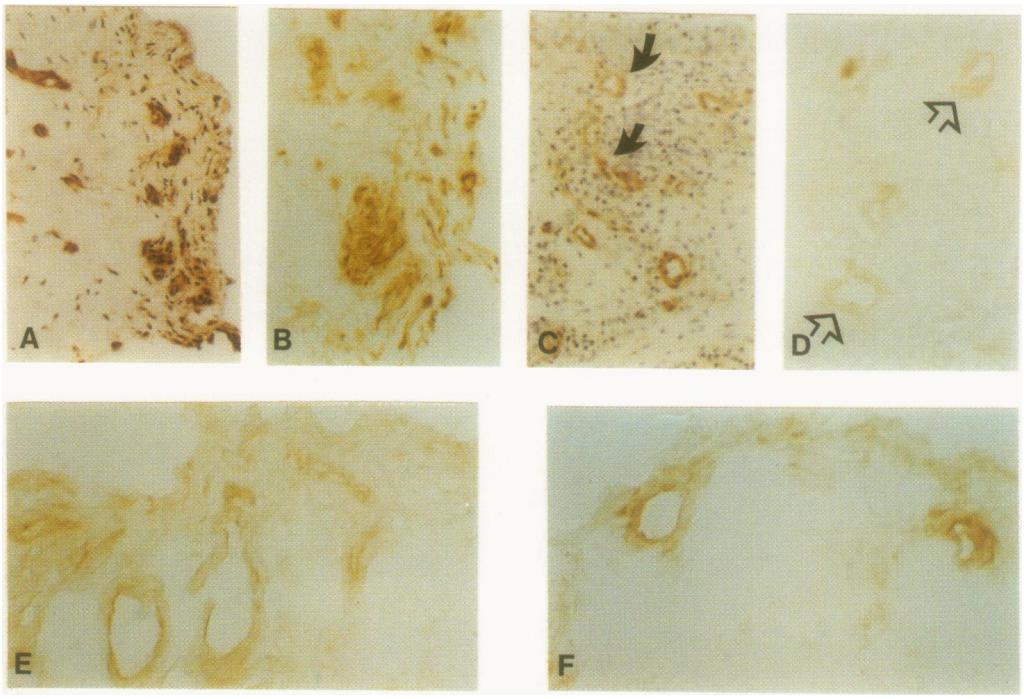

Figure 2 Expression of protectin (CD59), a cell membrane associated inhibitor of the membrane attack complex, in synovium in various arthritic conditions. (A) (Haematoxylin counterstain, ×125): general view of the CD59 expression in osteoarthritic (OA) synovial membrane, representing a set of chronic joint derangements [see table 2, exclude cases with rheumatoid arthritis (RA)]. (B) (No counterstain): consecutive synovial section as in (A), with ×315 magnification; note strong and uniform staining of the protectin in synovial lining cells, endothelium, and some synovial stromal cells. (C) (Haematoxylin counterstain, ×125): general view of CD59 expression in synovium with RA. (D) (No counterstain): consecutive synovial section as in (C), with ×315 magnification. (E) (No counterstain, ×315): synovium with flare up of OA. (F) (No counterstain, ×315): synovium with acute reactive arthritis. Note in these panels (in contrast to OA): (1) a weak endothelial staining for protectin in microvasculature (some indicated by arrows) in hyperplastic synovial intimal layer in RA; also, in synovium with acute arthritides, (2) absence of protectin staining in lining cells of hyperplastic synovium in RA, and weak protectin expression in synovial lining in acute arthritides. (ABC technique, frozen synovial tissue sections.)

important effector system in various arthritides.[2–10] On the other hand, it is conceivable that complement has—at least in part—different roles in different joint diseases. This possibility is supported by increased evidence of differences in the regulation of complement in rheumatoid arthritis and osteoarthritis[7] and also by the different susceptibilities of different cells to survive complement mediated damage.[14 22] Our study extends this approach by reporting a concomitant increase in complement turnover and a deficiency of protectin (CD59; the cell membrane associated inhibitor of the MAC) on the synovial cells in rheumatoid arthritis, and to a lesser extent also in many acute arthritides, but not in other joint diseases.

Local activation of the early complement cascade leads to an increase in synovial fluid levels of C3d/g and C3c,[2–5] fragments generated by proteolytic cleavage of C3b. The native C9 is an acute phase protein,[23] although its eventual cellular sources in synovium, if any, have not been identified.[24] Consumption of C9 from synovial fluid seems to follow an activation of the terminal complement pathway, TCC formation, and its deposition in synovium. In this study C3c and C9 were localised in order to assess complement turnover in synovial tissue. Rheumatoid arthritis and various acute arthritides—but not samples from joint derangements associated with degenerative or mechanical causes—showed relatively extensive and similar patterns of C3c and C9 deposition in synovial vascular and intimal compartments. This signifies complement activation and increased turnover. This can be explained by the presence of specific and persistent inductors of the complement, including rheumatoid factor containing immune complexes in rheumatoid arthritis. However, as suggested by the complement activation in acute arthritides, some non-specific mechanisms also seem to be able to activate the complement system. These may include tissue ischaemia and necrosis.[25] Activation of complement may also be initiated by proteolytic cleavage of C3 and C5 by activated plasmin and various proteinases released from neutrophils, mast cells, and macrophages,[26–28] and these cascades can be amplified by proteolytic and oxidative inactivation of proteinase inhibitors. It may also relate to other—as yet unestablished—factors, as it has recently been suggested that hyaluronate-protein complexes form during acute inflammatory reactions.[29]

Taken together, the present findings on C3c and C9 in the affected synovial membranes in rheumatoid arthritis are largely in accordance with the previous observations, where the deposition of both native and neoantigens of C3 and C9 (for example, C3b, iC3b, and TCC) has been localised.[8–10] The present findings extend these earlier observations into various acute arthritides and indicate that synovial intimal and endothelial cells are potential

targets of complement mediated damage. These and adjacent cells are permanently subjected to the systemic (blood) and local (synovial fluid) pools of the complement system, and their protection against accidental homologous lysis by MAC would therefore seem to be necessary.

Protectin (CD59), a 29 kDa glycoprotein, is constitutively expressed on haematopoietic and resident tissue cells throughout the human body.[30] CD59 is anchored to the cell membrane by glycosylphosphatidylinositol (GPI) linkage. It is suggested that CD59 may be involved in several immunological phenomena, although it is best known as an effective inhibitor of homologous complement lysis.[31] mRNA for CD59 has been extracted from normal and diseased human synovium, and mRNA encoding CD59 has also been detected in synovial fibroblasts, human umbilical vein endothelial cells (HUVEC), and lymphocytes, but not in monocytes.[24] Protectin was earlier localised by immunohistochemical means in synovial blood vessels.[9] The present study shows that it is also found in synovial lining and in some stromal cells, which is a new observation. It also appears that, in contrast to all the other chronic joint derangements studied, in rheumatoid arthritis synovial cells do not express protectin and that protectin expression is weak in many synovial stromal and endothelial cells. In addition, protectin expression seems to be partially lost in many acute arthritides. Factors regulating its expression are not known. Although some recent studies suggest that cytokines may be involved,[32] and that CD59 may be shed by exocytosis[33] or detached from its GPI anchor by GPI specific phospholipase C[34] or by proteolytic enzymes,[35] which might be responsible for the present observations on the aberrant expression of CD59 in diseased synovium.

There is indirect evidence suggesting that synovial cells in rheumatoid arthritis are subjected to MAC mediated attack.[14] Normally, this assembly is inhibited by a concerted action of soluble and cell membrane associated inhibitors.[1] Inefficient control of the MAC in the rheumatoid arthritis fluid phase has recently been suggested after relatively low levels of vitronectin and clusterin were found in rheumatoid arthritis synovial fluid.[7] These inhibitors bind to C5b-7 and block its insertion into the cell membrane. Protectin seems to interfere with the MAC assembly on the cells by interaction with C8 and C9,[36] the ratios of which seems to be critical for non-lethal effects of the MAC on synovial cells.[15] Thus, in line with the findings in synovial fluid, our present finding on the lack of protectin in synovial cells in rheumatoid arthritis suggests there is also inefficient control of the MAC in synovial tissue. This might predispose to synovial cell damage or to various stimulatory effects by MAC in rheumatoid arthritis, though according to our present observations this also occurs in many acute arthritides. In addition to a known deficiency of CD59 in paroxysmal nocturnal haemoglobinuria, an aberrant expression of protectin has also been found in numerous other conditions. It may play a role in endothelial and tumour cells in, for example, atherosclerotic lesions,[37] myocardial infarction,[25 33] malignancies,[32 38] systemic sclerosis,[39] and psoriasis.[40] These observations have raised the hypothesis that protectin expression may influence resistance of autologous or tumour cells to complement mediated lysis and removal of the tissue debris after damage. It seems, therefore, that our observations on aberrant protectin expression are not specific to synovial tissue or synovitis.

We conclude that activation of the terminal complement pathway and evidence of lack of protectin in synovial or endothelial cells in rheumatoid arthritis and in various acute arthritides may make them amenable targets for MAC mediated effects.

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