Zeitschrift: Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften = Bulletin de l'Académie suisse des sciences médicales = Bollettino dell' Accademia svizzera delle scienze mediche

Herausgeber: Schweizerische Akademie der Medizinischen Wissenschaften

Band: 35 (1979)

Artikel: Collagenase and prostaglandin in connective tissue destruction : cell-cell and humoral interactions

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DOI: https://doi.org/10.5169/seals-309098

Bull. Schweiz. Akad. Med. Wiss. 35, 329-343 (1979)

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COLLAGENASE AND PROSTAGLANDIN IN CONNECTIVE TISSUE DESTRUCTION: CELL-CELL AND HUMORAL INTERACTIONS

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Summary

Connective tissue destruction is a major characteristic of chronic rheumatoid arthritis (RA). This process is accompanied by local cellular and humoral inflammatory reactions. Long-term cultures of adherent synovial cells (ASC) from patients with RA produce large amounts of collagenase and prostaglandin (PGE_2), two substances that play a role in the degradation of joint structures. Levels of collagenase and PGE_2 can be stimulated (up to several hundred-fold) with a soluble factor (MCF) from cultured peripheral blood mononuclear cells (MW ~14,000). The monocyte-macrophages alone produce MCF but can be stimulated directly with Fc fragments of immunoglobulin or concanavalin A to increase MCF production. Addition of T lymphocytes in the presence of lectin or antigen significantly enhances the production of MCF. MCF affects other biological processes in synovial cells such as the rate of collagen synthesis, cell proliferation and sensitivity to PGE_2 as well as collagen itself can further modulate collagenase release by the synovial cells and function in an amplificative loop. The understanding of these interactions between cells, mediator-effector substances and connective tissue substrates may provide a basis for devising more rational approaches to therapy of the destructive lesions which characterize RA.

Résumé

La destruction du tissu conjonctif est l'une des principales caractéristiques de l'arthrite rhumatoide (AR). Ce processus s'accompagne de réactions inflammatoires cellulaires et humorales. Des cultures à long terme de cellules synoviales de patients AR produisent de grandes quantités de collagénase et de prostaglandine (PGE_2), deux substances qui peuvent

jouer un rôle dans la dégradation des structures articulaires. Le niveau de collagénase et PGE_2 peut-être augmenté de plus de 100 fois par la stimulation d'un factor soluble (MCF: mononuclear cell factor) obtenu de cultures de cellules mononuclées du sang (PM~14.000). Les monocytes-macrophages produisent spontanément le MCF, mais la production de ce dernier peut-être augmentée par des agents tels que les fragments Fc d'immunoglobulines ou la concanavaline A. De même, l'addition de lymphocytes T en présence de lectines ou d'antigènes augmente la production de MCF. MCF induit d'autres processus biologiques dans les cellules synoviales telles que la synthèse du collagène, la prolifération cellulaire et la sensitivité des cellules à un changement du contenu de l'AMP cyclique. Des produits libérés par les cellules synoviales, tels que la PGE_2 ou le collagène, peuvent eux-mêmes moduler une production ultérieure de collagénase par les cellules synoviales. La compréhension des interactions entre les cellules et les substances jouant un rôle de médiateurs et d'effecteurs, ainsi que l'interaction avec la matrice extracellulaire offre une base permettant une approche plus rationnelle de la thérapeutique des lésions destructives qui caractérisent l'arthrite rhumatoïde.

Connective tissue destruction is a major characteristic of chronic rheumatoid arthritis (RA). This process is accompanied by local cellular and humoral inflammatory reactions, involving cellular infiltration and proliferation. Production of a variety of mediator and effector substances by this inflammatory cell mass presumably regulate the destruction or new synthesis of extracellular matrix. In addition, systemic manifestations occur, reflecting generalized immunologic or biochemical abnormalities.

Although the ultimate cause of RA is unknown, various steps in the pathogenesis can be examined such as the enzymatic mechanisms leading to the destruction of articular structures. Morphological observations of the pannus-cartilage junction in RA are consistent with active resorption of cartilage and bone by the hyperplastic pannus. The destructive process seems to occur in a narrow zone less than 3 µm wide which separates the inflammatory cells from cartilage or bone. This zone contains amorphous material and degraded collagen fibers and is presumably the site where extracellular breakdown of collagen occurs (1). The histological appearance of the pannus is characterized by organized aggregates of lymphocytes, monocytes, macrophages, fibroblasts, smooth muscle and endothelial cells in close contact with hyperplastic synovial cells, some of which are multinucleated. Polymorphonuclear leukocytes are usually scanty. It is uncertain whether the cells responsible for the resorption are derived from the bone or cartilage itself or from the hyperplastic inflammatory cell mass which continues to develop as the lesion progresses. The cell mass is heterogeneous and it is probable

that interactions among its different cells result in the modulation of a variety of cell functions, such as chemotaxis, proliferation, metabolism, synthesis and secretion of extracellular macromolecules and release of substances which are involved in the degradation of the extracellular matrix. It is also possible that cell products released by the pannus act on cartilage or bone cells to stimulate the resorptive process (39).

In vivo human studies of the mechanisms of extracellular matrix breakdown and cell-cell interactions are difficult, and animal models which do not reproduce all of the features of RA may not be pertinent when extrapolated to human pathology. Utilization of a human cell culture system, despite the restrictions of any in vitro model, provides an experimental tool for asking precise biological questions concerning the control of substances which presumably are involved in connective tissue destruction such as collagenase and prostaglandin.

We have previously shown that cultures of human RA synovial cells produce high levels of collagenase and PGE_2 (2). Considerable information has now been accumulated which establishes a role for collagenase in the destruction of connective tissues in inflammatory arthritis (3). Collagen degradation in RA is predominantly extracellular, consistent with evidence in vitro that collagenase is released from cultured tissues. Collagenolysis in vitro has been shown to be proportional to the collagenase activity released into the culture media. It has been demonstrated that the putative collagen substrates degraded in the course of rheumatoid synovitis are substrates for collagenase in vitro. Furthermore, it has been shown that a collagenase similar to that produced by cultured synovium has been detected in synovial fluid from subjects with inflammatory arthritis (4). Some of the activity in rheumatoid synovial fluid is of higher molecular weight than that of the enzyme in rheumatoid synovial cultures and is probably derived from the polymorphonuclear leukocytes in the synovial fluid (5).

Products similar to the specific reaction products of synovial collagenase that act on collagen in vitro have been demonstrated in vivo. Collagenase has been localized to the pannus/cartilage junction in RA by immunofluorescence using labeled specific antibody to synovial collagenase. Relatively little immunoreactive material has been demonstrated around cells distant from the edge of the cartilage (6).

The enzyme is active at neutral pH and specifically cleaves the intact helical collagen molecule at a locus three-quarters from the amino terminus. Vertebrate collagenase has a strong preference for collagen molecules in the native form; denatured collagen by comparison is a poor substrate. Although the collagen in its native helical conformation is resistant to many proteinases, once the first cleavage is made and the molecules solubilized, proteinases can further degrade the collagen molecule. Collagenase does not appear to be stored for

Table I. Characteristics of rheumatoid human synovial collagenase

- Molecular weight ~32,000
- pH optimum 7 - 8.5
- Secreted, not stored
- Cleavage across helices 3/4 from amino terminus between Gly-Ile residues in α1 (I) chains Gly-Leu residues in α2 chains
- Helical collagen cleaved at rate > denatured collagen
- Type I or III collagen cleaved faster than type II
- Inhibited by chelating agents, sulfydryl-containing compounds, α2-macroglobulin, β1 anti-collagenase, fibronectin, proteoglycans, various tissue inhibitors, cationic proteins, Platelet factor IV
- Latent enzyme activated by various proteases (trypsin, chymotrypsin, plasmin, kallikrein) and organic mercurial compounds

subsequent release (except in polymorphonuclear leucocyte (7, 8), but appears to be synthesized de novo and secreted either in a latent or active form. Some important biochemical characteristics of synovial collagenase are summarized in Table I (for references, see review 9).

Although collagenase in synovium was first detected in rheumatoid tissues (10), enzyme activity has subsequently been identified in cultures prepared from biopsies of synovium from other diseases including osteoarthritis (11), juvenile RA, hemophilic arthritis (12) and pigmented villonodular synovitis (9). The magnitude of collagenase production seems to correlate with the degree of proliferation of synovial cells and the vascularity of the proliferative lesion. The factors which control the pattern of growth and invasiveness of the proliferating cell mass present in RA synovium are unknown. An increased rate of proliferation of rheumatoid synovial cells has been suggested (13). It has also been shown that collagen or fragments of collagen can be chemotactic, and in the chronic phase of RA these products may participate in the recruitment of cells to the site of the inflammation (14). Mineralized bone collagen, however, cannot be attacked by collagenase (15). Only after the calcium-phosphate phase is removed, does the collagen become susceptible to collagenolytic cleavage. The mechanism by which the mineral is removed is not certain. Possibilities include chelators, local decrease in pH or production of a biological ion pump which would effectively reduce local concentration of these ions and favor dissolution of the solid phase (16). Cellular mechanisms are probably necessary for removal of the mineral phase and in model systems, substances such as osteoclast activating factor (OAF) have been identified which can accelerate bone cell mediated bone resorption (17) or polypeptide mediators

(CTAP) which can activate connective tissue metabolism and lactic acid production (18). Prostaglandins, particularly PGE_2, are produced in large amounts by rheumatoid synovium and have been detected in synovial fluid in vivo. Prostaglandins may have a number of effects on the inflammatory process and in addition may play a role in the process of bone resorption (19). Prostaglandins most appropriately belong to the mediator category. There is increasing evidence of the importance of PGE_2 as a mediator of inflammation (20). Depending upon the system, PGE_2 may have either a positive (inflammatory role) or negative (anti-inflammatory role) effect in the amplification loop of inflammation. Prostaglandins can increase production of certain lymphokines (22) and proteolytic enzymes (23), potentiate effects of other mediators such as bradykinin or histamine, and might stimulate or activate osteoclast activity. In other systems prostaglandins have been shown to inhibit cellular proliferation, immune responses, production of certain lymphokines and lysosomal enzyme release from polymorphonuclear leucocytes. Many of the effects of prostaglandins may be mediated by their effects on cyclic nucleotides. Other injurious effects of prostaglandins could result from the presence of highly reactive oxygen species (superoxide anion, hydroxyl radical, singlet oxygen), which are formed during the biosynthesis of prostaglandins (23).
The complex interactions which take place in the sequence of connective tissue destruction in RA are presented in Table II. In this destructive process "target tissues" or substrates are acted upon by a variety of "effectors" listed in the category of cellular or humoral factors. The activity of the so-called effectors are in turn regulated and controlled by a variety of "mediators" which may again be predominantly humoral or cellular in origin. Each component in the various compartments may interact to form a positive or negative feedback system. It is likely that the expression of all of these phenotypic functions are further influenced and altered by environmental and genetic factors.
Utilizing cultures of cells from rheumatoid synovium, some aspects of the complex interactions illustrated in Table II can be systematically approached.
Emphasis will be placed particularly on collagenase and prostaglandin (PGE_2), both of which have been shown to be produced by cells cultured from RA synovium. In order to study the mechanisms which control and regulate prostaglandin and collagenase production in RA synovium, we have developed the following cell culture system (2). Samples of rheumatoid synovium are initially treated with proteolytic enzymes and the dispersed cell population is maintained in culture. The population of cells (ASC) is heterogeneous. Many of these cells are large with a diameter often exceeding 30 μm. These cells frequently assume a stellate shape with abundant cytoplasm, several dendritic processes and large nuclei. They do not possess conventional macrophage markers such as immunoglobulin or complement receptors.

Table II.

	Mediators	Effectors	Target Substrates
Humoral	Complement, immunoglobulins	pH, organic acids	
	Lymphokines, Monokines (MCF, OAF, CTAP ...)	Active ion transport	
	Prostaglandins	Proteolytic enzymes	
	Plasminogen activator	(collagenase, cathepsins,	
	Proteases	elastase, hyaluronidase)	
	Kinins	Oxygen free radicals	
			Mineral Phase
			Proteoglycans
			Collagen
			Fibronectin
Cellular	Lymphocytes	Synovial cells	
	Monocytes	Macrophages	
	Polymorphonuclear	Polymorphonuclear	
	Platelets	Osteoclasts	
	Endothelial cells	Chondroclasts	
	Smooth muscle cells	Fibroblasts	

Furthermore, lysozyme activity, a macrophage product which is present during the first several days of culture, is not detectable after a week in culture despite persistence of the viable stellate cells. These cells release typical animal collagenase in large amounts (in early culture, up to 70 µg of collagen lysed/minute at 37°C (70 units)/10^6 cells/day). Some ASC continue to release detectable collagenase for prolonged periods (weeks up to >18 months). Since the cells have been cultured in medium containing serum it is necessary to pretreat the medium with trypsin, followed by excess soybean trypsin inhibitor to detect collcgenase activity. Large amounts of PGE_2 are also produced (up to 1200 µg/10^6 cells/day). With continued time in culture and after many passages by trypsinization and dilution, the magnitude of collagenase and PGE_2 release declines. Utilizing these cell culture systems it was found that indomethacin markedly inhibited PGE_2 production (ID_{50} 1 nM). In contrast, at this concentration, no significant change was observed for collagenase production. In some instances even an increase was found. Glucocorticosteroids inhibited (>90%) both collagenase and PGE_2 production at concentrations as low as 10 nM (ID_{50},1nM). Progesterone was inhibitory only at high concentrations ID_{50},10 mM). Of interest, however, was that when progesterone and dexamethasone were added simultaneously, the inhibition by dexamethasone of both collagenase and PGE_2 production was partially overcome by progesterone (25).
In addition to the predominant stellate cell, another small adherent cell is also present in

Table III. Effect of cocultivation of peripheral blood monocytes and synovial cells on collagenase production

Cell population		Collagenase Units/well (mean ± S.E.)
Monocytes cell density x 10^{-4}/0.5 ml	Synovial Cells	
100	10	7.9 ± 0.9
10	10	5.7 ± 0.8
2	10	4.8 ± 0.5
0.5	10	3.3 ± 0.5
0	10	0.1 ± 0.1
100	0	<0.01

the early synovial cultures. These small cells are frequently phagocytic and have immunoglobulin and complement receptors characteristic of macrophages. High levels of collagenase and PGE_2 persist in these early cultures even after the smaller monocyte-macrophage like cells have disappeared, suggesting that the larger cells have the major role in the production and release of these products. However, the gradual decline in PGE_2 and collagenase levels observed in later passaged cells suggests that these smaller mononuclear cells might regulate or modulate the production of collagenase and PGE_2 by the larger synovial cells. We reasoned that the macrophage might function as the mediator and not the effector cell in collagen destruction. Our observations that significant collagenase release had not been detected in unstimulated cultured human macrophages prepared by peripheral blood monocytes (0.05 Units/10^6 cells/day) added additional support to this hypothesis. Since macrophages do, however, produce significant amounts of PGE_2 (1-10 g/10^6 cells/day) it is possible that this substance plays a role as a mediator rather than effector in connective tissue destruction. The role of possible cell-cell interactions in regulation of prostaglandin and collagenase production was examined by co-cultivating purified populations of peripheral blood monocytes (Ficoll-diatrozoate gradient followed by sequential adhesion) with the synovial cells for 3 days and assaying collagenase in the culture medium as shown in Table III. Addition of monocytes at increasing cell densities was accompanied by an increase in stimulation of collagenase production.

That the increase in collagenase release is mediated at least in part by a soluble factor released by the monocytes into the culture medium is suggested by the results outlined in Table IV. Monocytes were incubated alone for 6 days at several cell densities and the medium from days 0 to 3 and days 3 to 6, removed and added to the synovial cells. The results in the co-culture suggest that the stimulation of collagenase release observed with

Table IV. Effect of Media from cultured peripheral blood monocytes on collagenase production by synovial cells

Media from cultured monocytes cell density x 10^{-4}/ml	day of culture	Synovial cell collagenase Units/well (mean ± S.E.)
10	0-3	11.6
	3-6	4.7 ± 0.8
2	0-3	11.3
	3-6	1.0 ± 0.3
1	0-3	8.0
	3-6	0.5 ± 0.2
0.5	0-3	9.4
	3-6	0.2 ± 0.1
0	-	0.1 ± 0.1

increasing concentrations of mononuclear cells is related to production of a soluble factor. To further understand and interpret the coculture experiments and studies with conditioned media we attempted to isolate and purify the product(s) responsible for the collagenase-stimulating activity.

The mononuclear cell factor (MCF) which stimulates collagenase and PGE_2 production by the synovial cells is reproducibly eluted from columns of Ultrogel AcA54 in a single sharp peak with an apparent molecular weight ranging between 10,000 and 20,000 and averaging about 14,000 (24, 26). A typical example is shown in Table V. Both PGE_2- and collagenase-stimulating activities have similar elution patterns on gel filtration. Experiments in progress indicate that MCF is eluted at concentrations of 0.05 to 0.10 M phosphate from columns of hydroxyapatite and at concentrations of 0.10 - 0.20 M NaCl, pH 7.4, from DEAE-52 columns. The MCF activity is resistant to trypsin but is destroyed by pronase. The MCF is retained in the supernatant fractions after precipitation of other proteins with 50% ammonium sulfate. Partial MCF activity is also retained after 30 minutes exposure to sodium dodecyl sulfate (SDS) and removal of SDS by dialysis. The factor thus shares many properties with the lymphocyte activating factor (LAF) produced by a murine macrophage line described by MIZEL et al. (27).

Studies involving separation of lymphocytes from monocytes suggest that monocytes are the source of the mononuclear cell factor. However, the monocyte also interacts with lymphocytes, particularly T lymphocytes, to produce the stimulating activity (28, 29). Purified subpopulations of mononuclear cells have been prepared utilizing techniques which separate cells based on adherence and phagocytic properties and the presence or absence of surface

Table V. Effect of partially purified mononuclear cell factor on collagenase production by synovial cells

MCF* dilution of column fractions in culture medium	Synovial cell collagenase Units/10^6 cells (mean ± S.E.)
1:10	11.6 ± 2.26
1:20	4.8 ± 1.44
1:40	1.7 ± 0.2
-	0.6 ± 0.1

* MCF represents the peak of activity from gel filtration on Ultrogel AcA54 followed by hydroxyapatite column

immunoglobulin (Ig). The purest populations of cultured adherent, phagocytic, surface Ig^- cells secrete collagenase and PGE_2-stimulating activity. These human monocyte-macrophages also secrete lysozyme at levels of 50 µg/10^6 cells/day and PGE_2 at about 10 ng/10^6 cells/day, but no detectable collagenase. The T lymphocytes obtained from Fab Sephadex affinity column effluents followed by passage through a nylon column to remove residual monocytes produce no lysozyme and only 1-2% as much collagenase- (or PGE_2-) stimulating activity. Although T cells produce very low levels of MCF, the addition of only 5% monocytes to the T cells in the presence of lectin increases the production of MCF by this mixed population. In some experiments, excess of T cells added to the monocytes has an inhibitory effect. This complex interaction between the T lymphocytes and the monocytes will require further investigation. It is likely that a delicate balance exists between subpopulations of T cells (helper or suppressor) and alterations in this balance (as in various pathological states) could modulate the production of MCF by the monocytes. In addition to T cell interactions, other factors may directly influence the ability of the monocyte to produce MCF. When purified monocytes in culture are exposed to Fc fragments of immunoglobulin or aggregated immunoglobulin, the production of MCF is increased in a dose-dependent relation. Similar results are also obtained with concanavalin A (31).

Of interest is the finding that Fc fragments and concanavalin A also stimulate PGE_2 production by monocytes (30). That the effect of concanavalin A and Fc fragments is not related to stimulation of PGE_2 production by monocytes is suggested by the failure of indomethacin which blocks PGE_2 production to affect MCF production (31). Since the synovial cell products released in culture may not be removed or diluted at the rate that they would be in vivo, it is possible that these products could themselves affect collagenase release by the synovial cells. Even in vivo it is possible that at the site of the inflammation high con-

centrations of various cell products could alter the behavior or activity of surrounding cells. Prostaglandins produced in small amounts by the monocytes and in higher quantities by the synovial cells could play a role in the regulation of the mediator system (modulation of immune reactions) as well as on the effector system (proteolytic enzyme release).

Since MCF increases PGE_2 production by synovial cells and since PGE_2 activates adenylate cyclase and increases the content of cAMP in synovial cells, the effects of MCF on cAMP content of synovial cells was examined (32). MCF did not directly increase the level of cAMP in the synovial cells. However, after 6 hours of exposure to MCF the cAMP levels in the synovial cells did increase. The first detectable increase in cAMP content corresponded to the time (6 hours) at which the first measurable rise in PGE_2 levels in the medium was noted, suggesting that the increase in cAMP content was secondary to PGE_2 stimulation of adenylate cyclase. Levels of cAMP then returned to baseline over the next 2-3 days despite the continued presence of PGE_2. When the synovial cells were incubated with indomethacin alone or indomethacin plus MCF, PGE_2 release in the medium was blocked and no cAMP increase could be detected. Of great interest was the cAMP response to further exogenous PGE_2 in the synovial cells previously exposed to MCF. When the synovial cells were exposed to PGE_2 after MCF preincubation no increase in cAMP content was detected. This finding suggests that high PGE_2 levels produced by prior treatment with MCF altered the ability of the cells to respond to PGE_2. The high concentration of endogenous PGE_2 induced by MCF "down regulated" or "desensitized" the cells to PGE_2. In synovial cells pretreated with indomethacin, PGE_2-induced cAMP responses were greater than in cells preincubated with culture medium alone. The diminished PGE_2 induced cAMP response in the non-indomethacin treated cells likely represents desensitization of the cells by endogenous PGE_2 produced during the preincubation. A suprising finding was the enhanced PGE_2-induced cAMP response in cells incubated with MCF plus indomethacin. The increase exceeded that seen with indomethacin preincubation alone. This suggests that MCF may actually sensitize ("up regulate") the cells to PGE_2, possibly by increasing the affinity or number of PGE_2 binding sites.

The MCF not only altered the cAMP response to PGE_2, but in addition MCF affected the rate of proliferation and magnitude of (^{3}H)thymidine incorporation by the synovial cells (32). In synovial cells incubated with MCF, studied in the log phase of growth when PGE_2 levels were high (secondary to stimulation with MCF) a consistent inhibition of cell proliferation was observed. These inhibitory effects of MCF appeared to be related to the increased PGE_2 released by these cells since indomethacin blockade of endogenous PGE_2 production reversed the inhibitory effects of MCF. In fact, as in the cAMP studies, cell pro-

liferation and (^{3}H)thymidine incorporation were greater in MCF- plus indomethacin-treated cells than in indomethacin treated cells, suggesting that the MCF has a mitogenic effect on the synovial cells. A pattern similar to that described for the cAMP response to PGE_2 and cell proliferation was found for protein and collagen synthesis. Synovial cells exposed to MCF plus indomethacin produced more collagen (type I and III) in comparison to cells exposed to indomethacin alone (33).

We have also detected interactions between collagenase and PGE_2 production in the synovial cell cultures (29). Indomethacin in the presence or absence of MCF consistently inhibited PGE_2 production. Inhibition was complete at concentrations of indomethacin greater than 10 - 50 nM. However, collagenase release by the cells was only slightly decreased at the higher indomethacin concentration and in some cultures was actually increased in the presence of low concentrations (1 nM) of indomethacin. There were, however, two patterns of collagenase response observed in cells exposed to MCF in the presence of indomethacin. In some, indomethacin did not alter collagenase production, despite marked inhibition of PGE_2 production. In others, indomethacin blunted collagenase response. In all instances in which a decrease of collagenase resulted from exposure to indomethacin, addition of exogenous PGE_2 restored collagenase production to levels attained with MCF alone. WAHL et al also noted inhibition of collagenase production by indomethacin in endotoxin-stimulated rodent macrophages. They were able to overcome this inhibition with low doses of exogenous PGE_2 or dibutryl cAMP (22). Based on these findings, we have developed a model for the types of cellular and hormonal interactions which may occur in the synovitis of RA. These interactions ultimately determine the outcome of the proliferative lesion and the magnitude of the connective tissue destruction (Figure 1) which characterizes this disease. The dashed lines represent positive or negative feedback. Recent work in progress suggests that collagen or fragments of collagen could either act on the synovial cells to increase collagenase production (34) or act on the mononuclear cells to modulate MCF production (38). Types II and III collagens have been found to stimulate production of leukocyte migration inhibition factor by mononuclear cells from peripheral blood of RA patients (36) and a lesion resembling adjuvant arthritis has been produced in rats injected with type II collagen in incomplete Freund's adjuvant (37). It is also possible that the collagen and its product are responsible in chronic inflammatory states for an amplification loop independent of any immune mechanism since some cells have been shown to have collagen receptors on their surface. Thus, the cells present in the rheumatoid synovium may be thought of as an effector system which acts on connective tissue substrates to produce the destructive changes characteristic of RA. Our findings suggest that mononuclear cells present in rheumatoid synovium may function as

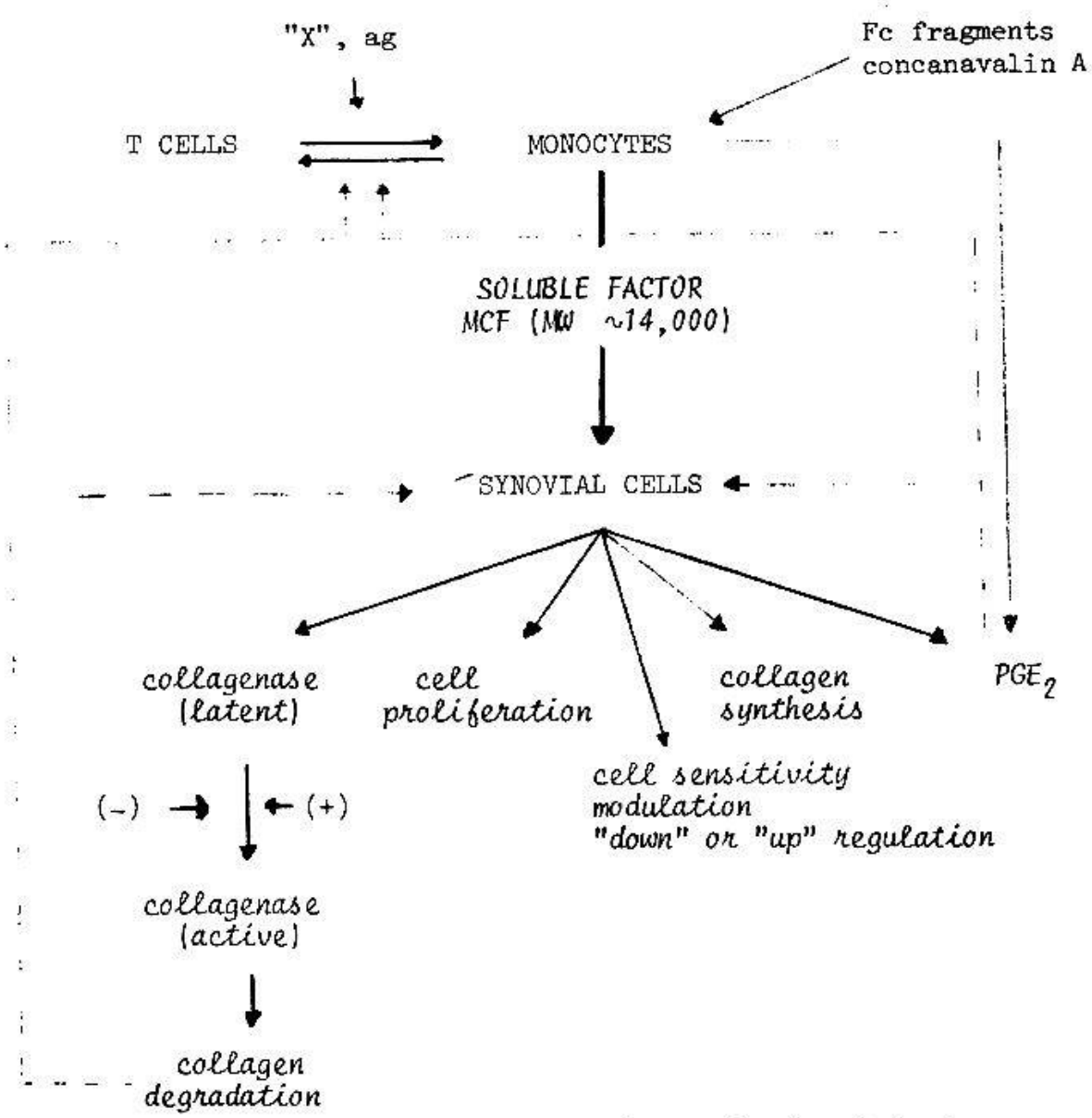

Figure 1. Possible sequences in pathophysiology of connective tissue destruction

mediators (humoral and cellular) which interact with synovial cells to alter a variety of synovial cell functions including proliferation and matrix formation. This interaction results directly in the production of substances such as collagenase and PGE_2 which are involved in degradation of the extracellular matrix. At a local level, in the inflammatory lesion, one could consider many of the events in terms of a microendocrine system in which the final biologic responses are controlled by receptor-ligand interactions between mediators and the effector system. The capacity to respond to various mediators such as the prostaglandins may be altered by factors such as MCF which change the affinity or binding properties of the effector system for the ligand. Drugs such as indomethacin may exert their effects on many

of the steps in the inflammatory process. Furthermore, depending on the stage of the lesion, the sensitivity of the effector system to mediators may change markedly and the final biologic results may be dramatically different. Further understanding of the interactions between the mediator-effector system and specific interactions with connective tissue substrates may provide a basis for devising more rational approaches to therapy of the destructive lesion which characterizes RA.

Acknowledgements

This work was supported by U.S.P.H.S. grants AM-4501, AM-3564 and AM-7258. J.-M. Dayer has also received support from the Fonds National Suisse de Recherche Scientifique. We are grateful to D. Bastian, W. Karge, M. Roelke and E. Schmidt for technical assistance and to J. Hodges for preparation of the manuscript.
This is publication No. 774 of the Robert W. Lovett Memorial Group for the Study of Diseases Causing Deformities.

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