The Pathogenesis of Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is due to a combination of phagocytosis and anaphylaxis gone awry. Immune complexes create their havoc via Fc gamma III receptors that signal via the tyrosine phosphorylation immunoreceptor pathway. Anaphylatoxins, mainly C5a, signal via the MEK kinase cascade, and both engage in cross-talk via NF kappa B. Aspirin-III blocks signals sent by both: immune complexes via FCR, and anaphylatoxin via C5 receptors. Drugs that affect both pathways, for example anti-B cell monoclonal antibodies, such as rituximab, and anti-C5 monoclonal antibodies, such as pexelizumab are currently being investigated.

We now appreciate that cytokines are important mediators of inflammation in RA but are downstream of the primary insults: immune complexes and anaphylatoxins. We can therefore begin to ask what the antigen or antigens might be that produce IgGs reactive to 7 S or 19 S rheumatoid factors. The primary antigens of RA could well be CPs, formed perhaps by oral bacteria. Once immunoglobulins become recognized by rheumatoid factors, immune complexes form, and these activate anaphylatoxins. Phagocytosis and anaphylaxis are the proximal events of RA.

Rheumatoid arthritis (RA) is a systemic disease that cripples patients by progressively destroying cartilage and bone. It is initiated by immune complexes and complement, perpetuated by cytokines, and effected by metalloproteinases. RA begins as an acute Arthus-like inflammation in the synovial fluid, in which IgM and IgG rheumatoid factors (anti immunoglobulins) are present in serum and in the joints. Antibodies to citrullinated peptides (CP) are also present in serum and joints. Complement is activated within the synovial fluid, and the most important complement components in the fluid are the C3a and C5a anaphylatoxins.

The synovial fluid is rich in the RA cell, which is a polymorphonuclear leukocyte that has encountered and engulfed immune complexes and complement. Chronic inflammation of the hypertrophic synovium, on the other hand, is maintained by clusters of activated lymphocytes, mononuclear cells, and islands of plasma cells that make IgG and IgM rheumatoid factors directed against altered IgG. Together with invasive mesenchymal cells, these form the pannus that invades and destroys cartilage.

Activated mononuclear cells and endothelial cells within the pannus produce the cytokines of the Th1 and Th2 repertoire at various times and proportions. Some antibodies to these, such as against IL-1 or TNF or their receptors, are extremely effective at blunting the disease. Finally, cartilage is eroded due to the action of secreted metalloproteinases. While some of these half-dozen or so proteinases are released via an exocytic mechanism, which we have called “regurgitation during feeding,” others are released by mechanisms not yet described. The end result is RA with bone erosion, and the local lesions of RA resemble those of aggressive periodontitis in the mouth.

Moreover, as has been known since 1899, rheumatoid inflammation responds to high doses of salicylates, 4 to 6 g/day, which amounts to a millimolar concentration of salicylate in the blood. You need more than the micromolar concentrations achieved by the “take two aspirins and call me in the morning” dosages (<2 g/d, or aspirin II) to get relief from RA inflammation. Lower doses (i.e., <2 g/d)
relieve pain but not inflammation. The requirement for millimolar doses (what we’ve called aspirin III) should tell us something about what is going on in the joint.

**The Antiquity of RA**

How long has RA been around? Despite arguments to the contrary, mainly from San Diego, RA is not an old disease. Paintings that claim to show RA, those of Jakob Jordaens, specifically, show gout and/or baroque floursishes. Indeed, RA has only been around since the middle of the 19th century. It was first described by Sir Alfred Baring Garrod in 1859: “Although unwilling to add to the number of names, I cannot help expressing a desire that one might found for this disease, not implying any necessarily relationship between either it or gout and rheumatism.”

Why gout and rheumatism? Because those are the two rheumatic diseases that were NOT new in the middle of the 19th century. English physicians of the 19th century were not imperceptive, and when they named a new disease, we can accept that it was noticeably different from acute rheumatism and from gout. Garrod, of course, became famous for his description of gout and its cause. He was well known in London for sending his gouty carriage-trade patients abroad to “take the waters” uncontaminated by lead. Indeed there is a street named “rue Sir Alfred Garrod” in Aix-les-Bains, France.

The first person to describe rheumatism, or rheumatic fever as we now call it, was Guillaume de Baillou, who in the 17th century described the disease and distinguished it from gout, a disorder known in classical times. The distinction between gout and rheumatic fever was best drawn by Lord Chesterfield in 1765: “Gout is the distemper of a gentleman; whereas rheumatism is the distemper of a hackney-coachman… who is obliged to be out in all weathers an at all hours.”

This was a clue that rheumatic fever was due to infection: one caught it in bad weather, or in a coachman’s hovel. A gentleman acquired the “honor of gout” from drink. The social history of disease is one guide to pathogenesis.

**RA Is an Immune Complex Disease**

My generation of rheumatologists has established that RA is an immune complex disease. I refer to the work of Dan McCarty, Henry Kunkel, E.C. Franklin, Jakob Natvig, Nathan Zvaifler, and Mart Mannik. Indeed, I’ve echoed Garrod to argue that:

Although I am unwilling to add to the number of explanations, I cannot help suggesting RA is caused by an agent as well defined as either gout or rheumatism. Gout is due to monosodium urate crystals induced by lead, drink, or genetics. Rheumatic fever is caused by the beta-hemolytic streptococi by immune mechanisms that we still do not understand. Rheumatoid arthritis, I insist, is caused by immune complexes and complement.

Questions remain: what sort of immune complexes, directed against which antigens? Most would agree that complexes of 7s IgG or 19s IgM rheumatoid factors directed against altered 7s IgGs - of self-assembling 7s IgGs (Mannik) activate anaphylatoxins in the joint. Cytokine and metalloproteinase release follows engagement of Fc gamma and C5a receptors on phagocytes and synovial lining cells.

**Phagocytosis and Anaphylaxis**

RA is therefore the end result of defensive mechanisms gone awry: phagocytosis and anaphylaxis, innate and adaptive immunity. The cells of innate immunity, the phagocytes or eating cells were first described in starfish by Elie Metchnikoff in 1883, and the active humors of adaptive immunity the anaphylatoxins, were described by Charles Richet in 1901. Both of these discoveries resulted in Nobel Prizes.

Metchnikoff, working by the Straights of Messina, found that: “a splinter introduced into the body of a star fish, larva, becomes surrounded by motile cells as is to be observed in a man who runs a splinter into his finger…” He also found that bacteria could elicit the same reaction. “Bacilli also set up an exudative inflammation which brings up a large number of leukocytes to the point menaced.” We now know that bacteria and splinters are recognized as foreign bodies and are opsonized by components of complement. Anaphylatoxins, such as C3a, C5a—complement split products—were also a product of marine biology. Charles Richet, a good friend and fellow physiologist of William James, was invited in 1901 on a cruise aboard the Yacht of Prince Albert of Monaco: “The Prince advised me to study Physalia poisoning.” Physalia are jellyfish found off the coast of Monaco. But when Richet “came back to [northern] France and had no more Physalia to study, I hit upon the idea of studying actinia, [the sea anemone], which can be obtained in large quantities on all the rocky shores of Europe.” (By Europe, Richet meant Brittany and the Atlantic as opposed to the Mediterranean, where warm-water jellyfish abound.) “Actinia has a slowly acting poison. Three or more days must elapse before it can be known if the dose be fatal or not.” Here comes anaphylaxis: “An unexpected phenomenon arose, which we thought extraordinary. A dog when injected previously even with the smallest dose (5 mcg/kg), immediately showed serious symptoms: vomiting, bloody diarrhea, syncope, unconsciousness, asphyxia, and death.”

This was systemic anaphylaxis, from substances released when antigen (the toxin of Anemone) met antibody in animals “injected previously.”

But, what about local anaphylaxis, a reaction more
pertinent to RA with its joint effusions awash in immune complexes and complement? That was discovered by N-M Arthus a Marseille physiologist in 1903. Arthus found that when one repeatedly injected material such as horse serum into the skin of a rabbit, an increasingly severe form of inflammation ensued: he called it “local anaphylaxis.” And by the 1960s thanks to Frank Dixon and Charles Cochrane of the Scripps, it had become clear that both anaphylatoxins and neutrophils were required to produce the lesion. Animals deprived either of complement or neutrophils were resistant to local anaphylaxis à la Arthus.

In 1905, an Austrian pediatrician, Freiherr Clemens von Pirquet, later dean of the University of Vienna Medical School, warned that “The conception that antibodies, which should protect us from disease, are also responsible for disease, sounds at first absurd…” But he worked out that serum sickness was due not to antigens alone, not to antibodies alone, but to a complex of the two, which he called “toxic bodies.” “Clinical symptoms arise,” he noted “when toxic bodies form as antibodies and antigens disappear from the circulation.”

In 1971 Dorothea Zucker-Franklin, Bob Zurier, and I showed that in the joint, such immune complexes (toxic bodies, indeed) were picked up by neutrophils, to form the RA cell. Neutrophils phagocytosed immune complexes via Fc and complement receptors, phagolysosomes formed, and in the process of feeding, the cells regurgitated their lysosomal hydrolases to reproduce the lesions of the acute Arthus phenomenon.

**Antibodies as Autoantigens**

What turns immunoglobulins into antigens that are recognized by rheumatoid factor? Answers: a) partial denaturation, as by heat, b) reaction with an antigen via F(ab)2s, or self aggregation.

When normal IgG is heated at 62°C for 10 minutes, the IgGs aggregate with their Fc regions interacting one with another. These aggregates can now be recognized as “antigen” by IgG or IgM rheumatoid factors. The heated IgGs reveal hydrophobic areas at their hinge regions and can now interact with other hydrophobic proteins and with naked lipid membranes. When Ed Franklin and I exposed aggregated IgG to liposomes as hydrophobic lipid surrogates, the complexes induced over 80% leakage of sequestered material, while native IgG was inert. We confirmed this reactivity by means of electron spin resonance spin-label studies employing 16-doxyl stearic acid. Indeed, recent studies by Zitterkopf and colleagues have shown that immune complex disease in animals is associated with presence in the circulation of immune complexes with exactly these hydrophobic properties. The size and type of aggregate was important, with 15S to 22S clusters of IgG1 and IgG4 being the most active, while other IgGs and IgMs were inert. Recent crystallographic studies also showed that rheumatoid factors recognize IgGs ready to react with Fc receptors. That is because engagement of F(ab)2s by antigens will cause Fc portions of the same molecule to rearrange, ready to engage the Fc receptor.

**Fc and C5a Receptor Signals**

How does the engagement of Fc receptors activate inflammatory cells to respond? There are, of course, several classes of Fc receptors, and as we know from studies of animal knockout models, FcR3 is the dominant receptor that mediates joint inflammation during immune complex arthritis. FcR2B inhibits both joint inflammation and severe cartilage destruction in immune complex arthritis. In fact, phagocytosis and anaphylaxis can be described in modern ligand/receptor language: phagocytosis sends signals via several Fc complexes, while C5a, the anaphylatoxin, acts to upregulate the number of activating receptors and downregulate the inhibitory FcR receptors. Anaphylatoxin and immune complexes work additively: that’s why C5-deficient animals are highly resistant to the induction of immune complex–induced arthritis. This is the basis for anti-C5 therapy in RA and other diseases. Anaphylatoxins, such as C5a, launch a powerful signaling cascade themselves via G protein–linked receptors. C5a provokes a release cascade of intermediate lipid mediators such as phosphatidilinositol 4,5, bisphosphate,PIP2, and diacetylgllycerol (DAG). The lipids signal, or augment, kinase and phosphatase signaling, involving MEK, MAP and Erk pathways, which are in turn regulated by DAG and PIP2. Calcium is then released into the cell to activate the cells to secrete cytokines from mononuclear cells and to secrete lysosomal enzymes if they are neutrophils. As Michael Pillinger has shown, whatever ligand is displayed to chemoattractant receptors, the activation of MAP kinase is directly related to the activation response of neutrophils. Obviously, if you inhibit this, you can inhibit intracellular activation.

**Immune Complexes and Cytokines**

Let us consider phagocytosis and anaphylatoxins vs cytokines in RA. Anti-cytokine therapy against TNF or IL1 is certainly effective in RA. But anti-C5 and anti-B cell monoclonal antibodies are also effective. Otherwise, rituximab would not be in use, and anti-C5 would not be in clinical trials for RA at present. However, cytokines do not initiate immune complex formation or activate complement, whereas immune complexes and complement induce synthesis and release of cytokines.

What could any logical person, let alone a rheumatologist, conclude from these facts? Conclusion: immune complexes come first.

**Why Rheumatoid Factor? Why Anti-CCP?**

Rheumatoid factors are certainly not specific for RA; they recognize immunoglobulins that have encountered
a variety of bacterial or viral antigens. They are found in high titers in patients with bacterial endocarditis, hepatitis C, and periodontitis. But, patients with RA also make antibodies to CP (measured as anti-cyclic CP, or CCP). Anti-CCP titers are more sensitive and diagnostic than rheumatoid factor titers in RA, and they also are better predictors than rheumatoid factor for progression of joint damage. Indeed, depletion of B cells by rituximab drops anti-CP titers much more than such depletion drops rheumatoid factor itself.

We have suggested that antibodies to CCP may be a clue to the cause of RA. Neutrophils, macrophages, and endothelium express peptidyl arginine deaminase (PAD), which citrullinates proteins and releases just a touch of nitric oxide. However, only one bacterial species that inhabits humans can citrullinate anything: Porphyromonas gingivalis. Indeed, Porphyromonas gingivalis, which we all carry in our mouths and which runs amuck in periodontal disease is the only prokaryote to make this enzyme. PAD can citrullinate the alpha and beta chains of fibrin to render them antigenic, and it has been suggested that fibrin or other proteins might be an autoantigen in RA.

We have formulated the hypothesis that, in a genetically prepared host, bacteria present in periodontal disease may be one stimulus for transforming IgGs directed against CP into auto-antigens. RA patients have a higher than usual incidence of periodontal disease, which is not due to the therapy of their disease. Genetic studies show that peptidyl arginine deaminase 4 (PAD4) is a rheumatoid arthritis susceptibility gene and that specific HLA DR subtypes are associated with both progressive RA and severe periodontitis.

Is there a historical clue to the relationship between these two chronic, bone-destroying forms of disease? Remember that RA is a 19th century disease, first recognized in the most advanced bourgeois societies of the day: England and France. Between 1765 and 1859, sugar from the Americas conquered England. The year 1765 was the peak of the unfettered West Indian sugar trade, and domestic sugar taxes were imposed in England. The British in 1764 leveled the sugar tax on American sugar and molasses exports. In 1773 at the time of the Boston Tea Party, not only tea, but also sugar was dumped overboard because of the British tax, which by 1771 had yielded Britain £326,000. Sugar was called the white gold of the upper class. By 1800 in England, sugar consumption reached 160 million pounds per year, and by 1815 the British sugar tax yielded £3,000,000! Sure enough, the middle classes had begun to take tea, and that is when RA was first noted by clinicians. In 1874 Gladstone abolished the sugar tax to bring sugar prices within the means of the ordinary citizens. Somewhere between 1815 and 1874, something happened as the result of all that sugar: periodontal disease. Dare we say RA as well?

Summary
Rheumatoid arthritis is due to a combination of phagocytosis and anaphylaxis gone awry. Immune complexes create their havoc via Fc gamma III receptors that signal via the tyrosine phosphorylation immunoreceptor pathway. Anaphylatoxins, mainly C5a, signal via the MEK kinase cascade, and both engage in cross-talk via NF kappa B. It turns out that aspirin-III blocks signals sent by both: immune complexes via FCR and anaphylatoxin via C5 receptors. Drugs that affect both pathways are in the works: anti-B cell monoclonal antibodies such as rituximab will affect one side of the coin, and anti-C5 monoclonal antibodies such as pexelizumab will work on the other. We now appreciate that cytokines are important mediators of inflammation in RA but are downstream of the primary insults: immune complexes and anaphylatoxins. We can therefore begin to ask what the antigen or antigens might be that produce IgGs reactive to 7 S or 19 S rheumatoid factors. The primary antigens of RA could well be CPs, formed perhaps by oral bacteria. Once immunoglobulins become recognized by rheumatoid factors, immune complexes form and these activate anaphylatoxins. Phagocytosis and anaphylaxis are the proximal events of rheumatoid arthritis.

Note
This presentation is an informal essay based on three published reviews and three experimental studies: