Editorial

Rheumatoid Factors: What Do They Tell Us?

The hemagglutinating activity of rheumatoid factors (RF) was first identified by Waaler in 1940[1] and these autoantibodies were named rheumatoid factor by Pike in 1949[2] due to their association with rheumatoid arthritis (RA), prior to the understanding that they were antibodies. Much has since been learned about these autoantibodies that bind to the Fc portion of IgG in the γ2–γ3 cleft, and yet many questions remain. In this editorial, and elsewhere[3], the role of RF in host defense is discussed in the context of infectious diseases, as well as their putative role in pathological processes associated with RA, Sjogren's syndrome (SS), and mixed cryoglobulinemia (MC) associated with hepatitis C virus (HCV) infection.

RF IN INFECTIOUS DISEASES

It has long been recognized that the RF response is transiently associated with many infectious diseases. IgG on its own as a monomer is not very efficient at inducing RF. Structural studies indicate that organisms with multiple epitopes spatially arrayed in a confined area and coated with IgG are efficient at triggering RF (Figure 1)[4,5], which explains why some microorganisms are more associated with a RF response than others. More central to the continual production of "pathogenic" RF, however, is a constant or relatively constant source of that antigen. Persistent microorganisms, such as viruses that establish latent or chronic infections, or bacteria prevalent in the environment (i.e., enterobacteria, or those associated with urinary tract infections) are attractive explanations for the sustained high titers of RF seen in the pathologic conditions such as RA, SS, and MC. Although there is speculation that HCV can induce the RF response, there are no reports of a specific HCV protein that is capable of inducing RF. Indeed 70% of patients chronically infected with HCV do not mount a sustained RF response.

There are many important points suggested by studies of RF in infectious diseases. In most cases the RF response is transient. The individual who makes RF in response to infection rarely develops acute arthritis, except in infection with viruses such as hepatitis B[6], and bacteria such as *Staphylococcus aureus*, associated with endocarditis[7]. It is interesting, however, that the incidence of RF (~35%) in the latter study of infectious endocarditis was similar in both groups with and without rheumatic manifestations, indicating that the RF is not a good marker of arthritis in this group of individuals. The presence of RF in individuals with acute infectious diseases, however, can be associated with transient arthralgia. The RF response in this setting is viewed as rarely being detrimental. In contrast, the RF response may actually be beneficial since RF contribute to the clearance of immune complexes by contributing to the formation of larger sized complexes. This facilitates their removal[8,9]. In addition, Lanzavecchia has shown that RF B cells are competent antigen-presenting cells and can help

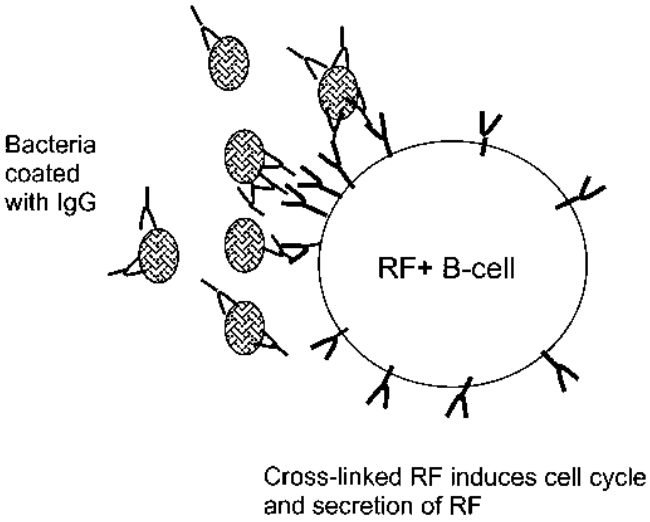

Figure 1. IgG-coated bacteria trigger RF+ B cells to undergo cell cycle and to secrete RF depending on the epitope density on the surface of the bacteria and the amount of specific IgG.

See Rheumatoid factor and antibodies to cyclic citrullinated peptide differentiate RA from undifferentiated polyarthritis in patients with early arthritis, *page 2074*

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stimulate the antipathogen response[10]. By processing the pathogen that was endocytosed because it was coated with IgG, the pathogen can be processed and peptides presented to T cells. Thus the net impact of the RF induced by the infectious agent is to contribute to the host defense.

In the general (healthy) population, the frequency of RF positive individuals ranges from 1.3–4.0% in Caucasians[11,12] to 30% in some tribes of North American Indians[13,14]. The frequency of IgM RF increases with age, whereas IgG RF frequency declines in the elderly[12]. The frequency of RF positive individuals in different infectious diseases depends on whether infection is primary or secondary and on the length of time the individual is infected (i.e., chronic carrier states). To illustrate this, in a study of patients with syphilis, only 8% of the primary infections were RF positive, whereas 23% of secondary infections and 37% of those latently infected were RF positive[13,15].

RF EXPRESSING B CELLS

Since the RF-B cell can act as an antigen presenting cell, there have been a number of studies investigating its phenotype. The small subset of B cells that express CD5, known as B-1a B cells, appear to produce RF and are enriched in the lymphomas of SS and the MC type II. Because the RF from the B1 B cells are usually of the IgM isotype and of low affinity, where less T cell help is implicated, it is likely that that lack of T cell input is in part the reason for the lack of isotype class switch and somatic mutation. In RA, the B1 B cells have been shown to be elevated in peripheral blood and have been shown to correlate with RF[16] as well as also being present in synovial fluid[17]. However, the high affinity RF found in RA and SS, where IgG and in particular IgA RF can be identified, appear to be produced by B2 B cells[18]. As discussed in a recent editorial, CD5 can have a negative regulatory role in the signal transduction from the B cell receptor[19], and its presence on B cells has been shown to diminish autoantibody production[20]. Defective regulation through CD5 could account for the sustained levels of RF observed in pathological conditions such as RA and SS.

From limiting dilution studies of the peripheral blood B cell pool, IgM RF expressing B cells are present in healthy individuals at a frequency of 0.9% (of total B cells), and in RA patients at a frequency of 1.48%[21]. Although the frequencies in peripheral blood are fairly similar, the RF in RA are monospecific whereas in the normal individuals they are polyreactive[21,22]. In synovial fluid the RF committed B cell frequency in seropositive patients is 10-fold higher[23]. Germinal centers can form both in the synovium[24,25] and in the liver[26]; however, the precise phenotype of the RF-B cells in the lymph nodes and tissue germinal centers is not known.

T CELLS IN THE RF RESPONSE

Many studies have illustrated the essential role of T cells in the class switch, where the cytokine production has an important impact on the type of Ig produced by the B cell[27,28]. IgM RF are the most studied and measured, due in part to the technical difficulty of detecting IgG RF; however, IgG and IgA RF have been identified and the latter in particular have been shown to be important in both RA and SS[29-32]. Both the processes of class switch and somatic hypermutation have been recently linked by a common pathway, a member of which is the activation induced cytidine deaminase[33]. From the studies of Schlomchik, *et al*[34], high affinity-RF-expressing B cells generated by somatic hypermutation are eliminated in normal mice, thus demonstrating a checkpoint in the control of this autoimmune response.

RF AND RHEUMATIC DISEASES

It is in the rheumatic diseases that RF (Table 1) are most studied, in particular in association with RA where ~70% of patients are positive for RF[43], and SS where ~40–50% are positive for RF (in primary SS)[45]. As well, the integral role of RF in MC (type II *and* III) has been in the spotlight in the past decade with the discovery of the HCV association. Cryoglobulins are classified according to the criteria of Brouet[65], where if they consist of a monoclonal antibody only they are classified as Type I. If the cryoglobulin is "mixed" and contains 2 or more Ig classes, it can be either Type II where one of the constituents is a monoclonal antibody, or Type III where only polyclonal antibodies are present. Both Type II and III MC are in reality cold perceptible immune complexes, and both can contain RF. Whereas patients with RA and the majority of SS patients have elevated and sustained levels of polyclonal RF, patients with MC (type II) and a small percentage of SS patients with lymphoproliferative disease can have a circulating monoclonal RF.

RHEUMATOID FACTOR IN RA

Whereas the frequency of RA is about 1% in white Americans and Europeans, and 4% in some tribes of North American Indians (NAI), such as the Pima[66], it is of interest that the frequency of RF also is higher in these tribes of NAI. From the genetic studies conducted to date the HLA locus is the most important genetic modifier[67,68] for both the disease and RF response[60,61]. In contrast to the sex bias to females in the overall susceptibility to RA, there appears to be a slight bias towards males for RF frequency and titer[43].

An important role for RF in diagnosis and prediction of RA pathogenesis has been clearly demonstrated. Three studies have shown that RF predate RA and that individuals with persistent high RF titers are at an increased risk of developing RA[69-71]. Two of the studies were cross-sectional and not in a genetically high risk population. As can be seen in Table 2, healthy individuals who have both IgA plus IgM RF (likely a reflection of the titer of RF) have a significantly

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Table 1. A comparison of rheumatoid factor in rheumatoid arthritis (RA), Sjögren's syndrome (SS), and mixed cryoglobulinemia (MC).

	RA	RA/sSS	pSS	Lymphoma in pSS	MC
Disease frequency	1–4% Caucasian[11,12] 30% N. Am. Indians[13,14]	Within RA 18–31%[35]	1–3% 1–7% HCV infected[36]	44 times rate of healthy population[37]	HCV 1.8–28%[38] MC in 30% of HCV+[39]
Female:male	7:3[40]	10:1[35]	9.5:1[41]	NA*	4:6[42]
RF frequency	70%[43]	86–90%[35,44]	40–70%[45]	50%[46,47]	~100%
RF biomarker for disease progression?	Yes[48-55]	NA	Yes[56]	NA	Yes[57]
Cryoglobulin frequency	38%[58]	NA	16%[59]	NA	100%
HLA/RF association	DR4[60-62]	DR4[34,35,43,44]	DR3[63]	NA	DR11[64]

* NA: not available. p: primary/s: secondary SS.

Table 2. The number of RF isotypes detected in serum of healthy individuals is a predictor for RA. Adapted with permission from Halldorsdottir, *et al*[71].

Individuals Positive for No. of RF Isotypes*†	RA Cases (%)	Followup Period, yrs	RA Annual Incidence, %
0, N = 36	0	16.1	0
1, N = 30	1 (3.3)	16.8	0.2
2 or 3, N = 54	6 (11.1)	16.7	0.67

* From a prospective health survey of 13,858 participants in the Reykjavik area since 1967[71].
† IgA, IgG, and/or IgM.

increased risk of developing RA compared to those with only one isotype of RF detectable in serum. In this issue of *The Journal* Jansen and co-authors[72] in a study evaluating the diagnostic value of RF and anti-cyclic citrullinated peptide (anti-CCP) in an early synovitis cohort, demonstrate that RF (when a cutoff of > 40 IU/ml is used) has a high specificity and acceptable sensitivity for predicting RA at one year, which is equivalent to anti-CCP in specificity and sensitivity. Moreover, they observe these biomarkers in different but overlapping subgroups of patients.

Of all the known RA biomarkers, RF consistently have been shown to be the best predictor of disease severity, in particular radiographic progression. This has been illustrated in many studies where patients have been followed from "early" synovitis for various periods of time[48-55] (see Figure 2).

RHEUMATOID FACTOR IN SS

The RF response is associated with SS, whether in primary disease or associated with RA or systemic lupus erythematosus. In the overall population primary SS is thought to be present in 1–3% of individuals, many undiagnosed. In RA, 18–30% of patients have secondary SS[35]. Complicating the issue of RF in SS is the HCV associated sicca syndrome, which can be diagnosed as SS (see below). RF appear to play an important role in the pathogenesis of pSS as they have been shown to be an indicator of the severity of salivary gland damage[56]. In addition, there is an increased risk of lymphoma in SS[73] with an incidence of 12.2 per 1000 person years[74]. The expansion of monoclonal RF has been demonstrated in a high percentage of the cases[46,47]. In a study of a large cohort of patients with primary SS, individuals who developed lymphoma had MC both at initial diagnosis of SS and at followup, thus indicating that the MC was a detrimental prognostic event[74]. In longitudinal studies, RF frequency was shown to increase in a Finnish population from 46% at baseline (time of diagnosis) to 74% at followup (medium time 10–11 years)[45]. In Caucasians with primary SS, HLA-DR3 has been shown to be a risk factor for the disease in patients who are autoantibody positive (59% were positive for RF)[63]. In secondary SS associated with RA, there is a 85–90% frequency of RF, with a female to male ratio of 10:1[35,44] and again as in RA the association is with DR4[63]. In primary SS, although rarely seen in men, the frequency of RF is higher in males[75], although clinical features are similar.

RF IN MIXED CRYOGLOBULINEMIA

Hepatitis C virus was first identified in 1989[76]. Of those infected with HCV, 68 to 73% are males[77]. About 30% of individuals infected with HCV develop MC[39,] and the population most at risk is female. The frequency of females with either type II or III MC is 63%[42], and of those with type II MC 71% are female[42]. Cacoub[64] has reported a significant association with HLA DR11 and MC, where DR7 was associated with protection against the production of MC. In

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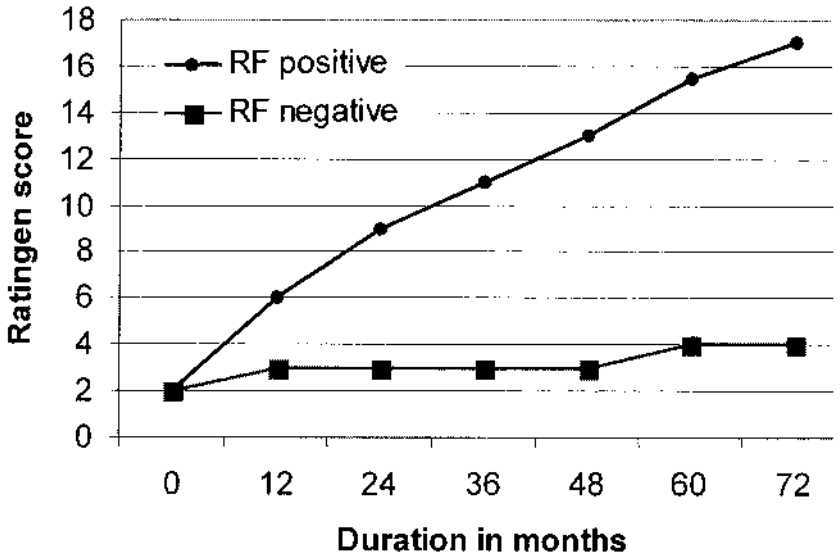

Figure 2. RA patients that are RF positive (n = 71) have a more rapid radiographic disease progression than those that are RF negative (n = 38). Adapted from Rau, *et al*, with permission[52].

contrast to RA, RF in MC appear to be a late event in HCV infection, being more frequent in those with more extensive liver damage[78].

The association between HCV and MC was first reported by Pascual in 1990[79], and has been the subject of many excellent reviews[42,80-83]. This cryoglobulin predominantly consists of complexes of RF bound to polyclonal IgG (enriched with anti-HCV IgG), which precipitates readily at 4˚C. The affinity of interaction between the RF and IgG is low at 37˚C but increases as the temperature drops[84]. The precipitation occurs at 4˚C due in part to the size of the complexes formed in the presence of calcium. It is conceivable that a decreased clearance of the MC (immune complexes that have activated complement and thus contain C3b), by the phagocytic CR1 expressing cells in the liver due to hepatitis contributes to their buildup in serum.

The MC in HCV patients is associated with serious extrahepatic disease features such as membrane proliferative glomerulonephritis, vasculitis, and sicca complex, which occur more frequently in females[57]. Because of the obvious overlap of the latter with possible SS, several studies have investigated the incidence of HCV in SS. In a review by Ramos-Casals[59] antibodies to HCV were detected in 14 to 19% of patients with primary SS. MC can occur in the absence of HCV, but less commonly[85,86]. MC have been identified both in patients with hepatitis B virus infection and in patients with alcoholic liver cirrhosis. It is possible that HCV and/or liver damage facilitates the induction of the RF that have the ability to form the cryoglobulins when complexed with IgG.

The germinal centers that form in the liver are a characteristic of HCV infection[26] and are likely the sites of induction of these RF. Very little is known about the hepatic RF response in the presence and absence of hepatic damage. Increasing evidence suggests that the cytokine bias of the T cell response to HCV determines the outcome of infection[87]. A Th1 response, characterized by interleukin 2 (IL-2), interferon-γ, and IL-12, is the prevalent cytokine pattern observed in patients who recover spontaneously from acute HCV. In contrast, Th2 cytokines, notably IL-4 and IL-10, dominate the response in patients with viral persistence and chronic HCV infections. Further, Th2 cytokines provide help for B cell activation, Ig production, and class switching. Thus, a T cell response, which would favor HCV persistence, would also tend to favor B cell activation and an increase in cryoglobulin production.

THERAPY AND RF RESPONSE

In patients with MC associated with HCV, the titers of RF fall in patients who respond successfully to PEG-interferon-α/ribavirin therapy[88], likely due to the increased health of the liver, and possibly the switch back to a Th1 response. In contrast in patients with RA who respond to therapy, most disease modifying antirheumatic drugs[89-91] as well as biologicals such as anti-TNF-α[92] are associated with a decrease in RF titer, which reflects the immunosuppressive and/or antiinflammatory nature of the therapy.

CONCLUSION

RF play an important role in the host response to many infectious organisms and contribute to the host defense by aiding in antigen presentation by RF+ B cells and to clearance of immune complexes.Recently it was shown that ligation of a Toll-like receptor along with the RF on B cells by IgG-DNA containing immune complexes was required for maximal activation and RF production[93]. Not only does this

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demonstrate an integral role for RF in the host response by utilization of a receptor important in the innate immune response[94] but also shows how tightly controlled this response is in normal individuals. In contrast, the sustained high-level RF response not only can predict RA disease but also can be a useful biomarker for specific disease features, such as radiographic damage in RA, and may contribute to the extrahepatic manifestations in HCV infection. It is likely that repeated infection and/or chronic infection contribute to the sustained RF response. Therapy can influence the RF response, and mechanisms that account for this include: immune suppression, antiinflammatory, or a shift in the type of T cells that influence the RF production.

MARIANNA M. NEWKIRK, PhD;
Department of Medicine,
The McGill University Hospital Centre,
The Montreal General Hospital, 1650 Cedar Ave.,
Montreal, QC, H3G 1A4, Canada.
E-mail: Marianna.Newkirk@mcgill.ca

Address reprint requests to Dr. Marianna Newkirk.

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