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Research Article

New Roles for Rheumatoid Factor

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In the 1940s, anti-IgG autoantibodies were discovered in the sera of patients with rheumatoid arthritis and given the term rheumatoid factors (RF).[1] The measurement of agglutinating IgM-RF is still the most useful serological test for the diagnosis of rheumatoid arthritis. High titers of IgM-RF are also present in primary Sjogren's syndrome, mixed cryoglobulinemia, and in several different chronic infections (1).

Recent advances in molecular and cellular immunology are gradually revealing the genetic and environmental factors that control RF production. Two sets of results were largely unexpected. First, genes encoding RF are present in most normal people, and their expression is carefully regulated during the development of the immune system. Second, lymphocytes with RF receptors on their plasma membranes are remarkably abundant in normal people, who have only low levels of circulating autoantibody. These data have suggested a new role for RF in the capture, processing, and presentation to T cells of antigens trapped in immune complexes. They may explain why RF production is sustained in patients with both rheumatoid arthritis and lymphoproliferative diseases.

Genetics of RF

The antibody molecule is composed of heavy and light chains that are encoded by genes on separate chromosomes. Aside from the diversity allowed by the pairing of two separate chains to form a heterodimer, each chain has a variable region capable of achieving tremendous diversity through the process of immunoglobulin gene arrangement.

The haploid human genome contains ~ 100–200 heavy chain variable (V) region genes, ~ 100 kappa light chain V genes, and an unknown number of lambda light chain V genes (2, 3). A functional light chain immunoglobulin gene is generated by the rearrangement in early B lymphocytes of one V gene to a separate joining (J) gene segment. In the case of the heavy chain gene, an additional gene segment, termed D for diversity, rearranges with the J segment before V gene rearrangement. This process, together with inaccuracies produced during VDJ and VJ recombination, and sequential somatic mutations in antibody V genes, produces a virtually unlimited array of different antibody molecules. Because immunoglobulin gene rearrangements and somatic mutations occur throughout life, self tolerance is *never* permanent at the B cell level. Autoantibodies can arise at any time. The important issues are (*a*) how the inherited repertoire of antibody genes influences the probability of specific autoantibody production, and (*b*) how the immune system prevents the expansion of self-reactive B lymphocytes.

Before gene cloning studies, indirect evidence suggested that RF autoantibodies may be part of an inherited immunoglobulin gene repertoire. First, it was observed that IgM paraproteins frequently have RF autoantibody activity. ~ 10% of Waldenstrom's macroglobulins are IgM RFs (4). Considering that the humoral immune system has the potential ability to generate millions of different antibodies, and that malignant diseases are generally considered to represent the chance expansion of a clonal lymphocyte population, the repeated occurrence of RF in IgM paraproteins is highly significant. Second, Kunkel demonstrated that 60% of IgM-RF paraproteins reacted with a polyclonal antiidiotypic antibody, termed anti-Wa (5). Idiotypes are antigens of the antibody variable region that can distinguish different immunoglobulin molecules. The finding that a high proportion of IgM RFs share a cross-reactive idiotype indicated that the variable regions of these antibodies are structurally similar.

Unequivocal proof that RF paraproteins are structurally related and are the products of a limited set of immunoglobulin V genes required (*a*) the generation of multiple different antiidiotypic antibodies against human RF light and heavy chains, (*b*) the sequencing at the protein or cDNA level of immunoglobulins that express the various cross-reactive idiotype(s), and (*c*) the isolation and analysis of the germline heavy and light chain V genes corresponding to these expressed sequences. The results of these studies, and of parallel investigations on anti-DNA antibodies, are summarized briefly in Table I (6–24). RF autoantibodies can be encoded by several different heavy and light chain V genes, each of which corresponds to a different cross-reactive idiotype. These results do not gainsay an important role for somatic mechanisms in the generation of RF autoantibodies. The salient point is that a few antibody variable region genes can account for more than half of all IgM-RF paraproteins.

Development of RF Precursors

Genetic characterization of RF-associated cross-reactive idiotypes made it possible to study the development and expression of RF precursors in normal life. Schroeder and co-workers reported that human fetal liver B lymphocytes transcribed only a small fraction of the total potential repertoire of human heavy chain V genes (25). Two of these expressed genes correspond to germline genes encoding RF heavy chains. Moreover, the major RF-associated heavy and light chain idiotypes are expressed by 10–30% of the B lymphocytes in the developing germinal

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1. *Abbreviations used in this paper:* CLL, chronic lymphocytic leukemia; D, diversity gene segment; HLA, histocompatibility molecule; J, joining gene segment; RF, rheumatoid factor; V, variable gene segment.

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Table I. Human Autoantibody Genes

Immunoglobulin V gene	Autoantibody association
Light chain	RF, antiintermediate filament, anti-low density
kv325	lipoprotein, cold agglutinins, anti-DNA
kv328h5	RF, anti-DNA
Vg	RF, anticardiolipin, cold agglutinin anti-DNA
lv117	RF, anti-DNA
Heavy chain	
hv1051	RF, anticardiolipin
hv3005	RF
1.9III	Anti-DNA
9-1	Anti-Sm
VH26	Anti-DNA, polyreactive
6-1G1	Polyreactive

The results are compiled from data reported in references 6–25.

centers of fetal human spleen (26). B cell lines derived from fetal lymphoid tissue may produce RF. Nonspecific stimulation of human umbilical cord B cells with Epstein-Barr virus, or the protein A molecule of *Staphylococcus aureus,* induces the release of abundant IgM-RF (27, 28). Collectively, these data indicate that the RF-related immunoglobulin genes are selectively rearranged and expressed early in immune development.

Although the data are still evolving, two phenomena apparently are responsible for the early development of RF-bearing lymphocytes. Humkv325, a V gene encoding the kappa light chains of many RFs, is abortively rearranged in B cells expressing lambda light chains, more commonly than can be attributed to chance alone (Rassenti, L., and T. J. Kipps, unpublished data). Lambda positive B cells do not coexpress kappa light chains. Hence, the high frequency of humkv325 rearrangement cannot be explained by antigenic selection. However, the light and heavy chain idiotypes that are highly associated with RF (17.109 and G6) often occur together on fetal B cells (26). Because heavy and light chains combine arbitrarily, and the coexpression of the two idiotypes usually indicates RF autoantibody activity, the latter results suggest that selection by antigen (or antiidiotype), as well as selective gene rearrangement, drives the early expansion of RF precursors.

RF Gene Polymorphisms and Autoimmunity

Immunologists have just begun to analyze systematically genetic polymorphisms in the RF-associated genes that are preferentially rearranged and expressed in fetal liver and spleen (29, 30). The two well-characterized RF-associated kappa light chain V genes (humkv325 and humkv328) are present in nearly all people, regardless of their ethnic backgrounds, and are not very polymorphic. In contrast, the RF-related heavy chain V genes (hv3005 and hv1051) are very polymorphic, and differ from person to person in both gene number and gene structure (30). At this point, we do not understand the evolutionary pressures that apparently keep the kappa V region locus relatively stable in the human population, in comparison to the heavy chain V region locus.

Recently, we have shown that the RF-related hv3005 gene is deleted in ~ 20% of patients with both rheumatoid arthritis and systemic lupus erythematosus, but in only 5% of normal subjects (30). The hv3005 gene is one of the most commonly transcribed heavy chain V genes in the developing immune system (25). The association between deletion of a major RF gene and autoantibody production seems paradoxical. However, as described below, the connection may be explained by the potential role of RF precursor B cells as regulators of antigen presentation and T cell activation.

Functions of RF B Lymphocytes

One driving force for the evolution of the humoral immune system must be the ability to resist infection with virulent microorganisms, particularly encapsulated bacteria. Preliminary results in humans and mice indicate that autoantibodies against IgG and DNA, and antibodies against bacterial polysaccharides, are structurally related and can utilize similar or identical V genes (31). The accumulated data from many laboratories also indicate that RF can amplify the humoral immune response to certain microorganisms. Although multimeric IgM-RF reacts weakly with monomeric IgG, the RF molecule may bind tightly to IgG aligned on a solid surface, such as a bacterial cell wall. For this reason, IgM-RF can stabilize the binding of the low-affinity IgG antibodies that are produced during an early polyclonal immune response to an infectious agent. The IgM-RF also promotes the clearance of IgG immune complexes. This role is particularly important for those IgG subclasses that do not readily fix complement.

Immune complexes which enter lymphoid tissues via the afferent lymphatics often localize to the marginal and mantle zone regions (32). Using the antiidiotypic antibodies as specific probes, we have recently shown that RF precursors are abundant in the mantle zones of tonsils and lymph nodes of people who lack the autoantibody in plasma (Fig. 1 and Axelrod, O., D. A. Carson, and T. J. Kipps, submitted for publication). Apparently, there is a complete discrepancy between the frequencies of B cells with surface RF and RF-secreting cells. It has been postulated that autoantibody positive B cells in normal adults serve no purpose, and have simply escaped clonal deletion. However, the high frequency of RF B cells in normal lymphoid tissue could provide a clue concerning a specialized function for this class of lymphocytes. We have considered the possibility that a major role of RF B cells is independent of antibody secretion, but rather relates to the antigen processing function of the mantle zone B lymphocytes.

The production of antibodies, particularly of the IgG, IgA, and IgE isotypes, usually depends upon helper T cells that release cytokines, which promote B cell proliferation and differentiation. Because T lymphocytes principally recognize peptide fragments bound to histocompatibility (HLA) molecules, much research in autoimmunity has focused on the comparative abilities of different HLA molecules to bind potential autoantigenic peptides. However, antigen presentation to T cells is also critically dependent on the unique specificities of B cell surface immunoglobulin. Indeed, it is the surface immunoglobulin molecule that ultimately dictates which antigens are captured and presented (33). Considering the localization of RF precursors in the lymph node mantle zone near the afferent lymphatic vessels, they may by particularly important for the processing of antigens trapped in immune complexes.

As mentioned earlier, autoantibodies probably appear intermittently throughout life, because somatic mutation of immunoglobulin genes is random and can give rise to virtually

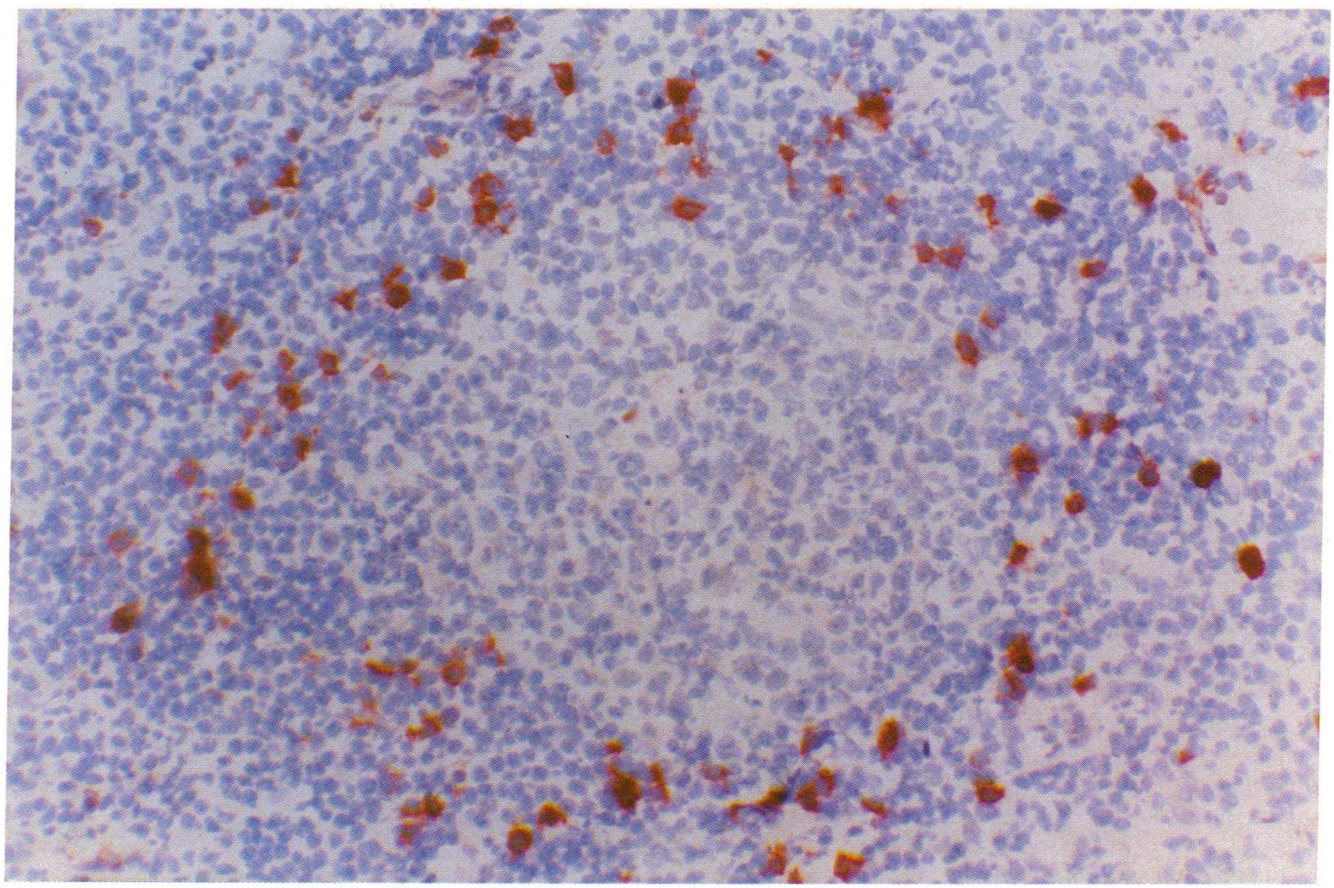

Figure 1. Human tonsil was reacted with monoclonal antibody 17.109, which recognizes an idiotypic antigen associated with RF light chains. Reactive cells were visualized with peroxidase-conjugated goat anti-mouse IgG. Note that the idiotype positive cells are very common but are confined to the mantle zones surrounding the germinal centers.

any antigen-binding specificity. Moreover, it seems highly unlikely that all T cells are nonreactive to the entire array of self peptides. Hence, a mechanism must exist to prevent the expansion of autoreactive B and T cells. Perhaps this function is fulfilled by the RF precursors in the mantle zone region. According to this hypothesis, spontaneously arising autoantibody-autoantigen complexes would be captured by RF precursors in the mantle zone. After antigen processing, the RF precursors would present self-peptides to autoreactive T cells, and in conjunction would release a T cell–inhibitory cytokine such as transforming growth factor beta (34). As a result, the antigen-specific T cells would fail to produce the growth factors necessary for B cell clonal expansion and differentiation. Although this hypothesis remains to be tested formally, it provides a logical explanation for (*a*) the early emergence of RF precursors during immune development, (*b*) the peculiar localization of these cells in the mantle zone, (*c*) the discrepancy between RF precursor frequency and RF synthesis, (*d*) the association between immunodeficiency and lymphoproliferation of RF precursors, and (*e*) the lack of expression of the common RF idiotypes in rheumatoid arthritis.

RF Expression in B Cell Malignancies

Chronic lymphocytic leukemia (CLL) cells frequently express both surface RF (35), and the RF-associated idiotypes (36–38). Although CLL is generally not an antibody-secreting tumor, the malignant cells can be induced to release small amounts of immunoglobulin in vitro. The released IgM has been demonstrated to have specific anti-IgG autoantibody activity in several instances (39). The CLL cells utilize autoantibody encoding germline V genes with little or no somatic mutation. In many CLL patients, there is an associated immunodeficiency state. These features of the disease are consistent with a clonal expansion of nonsecreting autoreactive B cells that regulate immune responses.

As opposed to CLL, the RF produced in Waldenstrom's macroglobulinemia, in Sjogren's syndrome, and by CLL cells that lack the CD5 surface antigen, often have heavy and light chain V region sequences that differ from the germline by as many as five to ten substitutions (40, 41). Considering that the kappa V regions are not polymorphic, the sequence differences presumably reflect somatic mutation events. Somatic hypermutation in antibody V genes has been estimated to occur at a rate of 10^{-3} to 10^{-4} per base pair per cell division (42). The eventual development of an antibody molecule with multiple somatic mutations therefore requires repeated antigenic selection and clonal expansion. RF precursor B cells must be exposed to immune complexes intermittently through life, and may be stimulated to divide and undergo somatic mutation whether or not the autoantibody is actually secreted. The exposure of human bone marrow B lymphocytes to hydroxyurea, an inhibitor of ribonucleotide reductase and hence of DNA

synthesis, selectively eliminates RF precursors without destroying the ability to generate nonspecific IgM or IgG after a polyclonal stimulus (43). This implies that RF cells often traverse the cell cycle. The continual cycling of RF precursor B cells may increase their chance for malignant transformation. Thus, the high frequency of RF among B cell neoplasms could be explained by (*a*) the high precursor frequency of RF B lymphocytes in the naive B cell repertoire; (*b*) ongoing antigen-driven proliferation of the RF B cell pool.

RF Expression in Autoimmune Disease

The RF produced in longstanding autoimmune diseases generally lacks the major cross-reactive idiotypes that are found on RF precursors in the mantle zone, and on RF paraproteins. Half of the IgM-RF paraproteins have light chains that derive from the minor kappa III V region subgroup. In contrast, immunoblot analyses of purified IgM-RF from rheumatoid arthritis synovial fluid reveal a distribution of light (and heavy) chain V region subgroups that is not strikingly different from total serum immunoglobulins (Silverman, G. J., and D. A. Carson, unpublished observation). Several different lymphoblastoid cell lines, and B-B hybridomas, have been established from rheumatoid synovial lymphocytes (44). These may display the same idiotypes and genes detected in CLL cells. However, the hybridomas may not be representative of RF-secreting cells in the patients. As noted earlier, normal individuals have a high frequency of RF B lymphocytes in the absence of autoantibody production. These cells can give rise to RF secreting hybridomas, even through they do not release the autoantibody in vivo.

Recent studies support a role for T cells in the generation of RF in rheumatoid arthritis. RFs of the IgG isotype are particularly abundant in the rheumatoid synovium, where they are produced locally. However, despite concerted efforts from this and other laboratories, T lymphocytes reactive with autologous IgG have not been detected in rheumatoid arthritis patients, or in mice producing autoantibodies. It therefore seems unlikely that the T lymphocytes which trigger RF class switching recognize epitopes in the Fc fragment. More likely, the T cells that facilitate the IgM-RF to IgG-RF class switch react with an antigen in an immune complex, that is bound and processed by RF precursor B lymphocytes. An increase in the frequency of RF precursor B lymphocytes accompanies anamestic immune responses in humans and animals, although large amounts of the autoantibody are not usually released into the circulation (45, 46). The expansion of RF precursors during secondary immune responses is controlled by T lymphocytes that recognize antigen trapped in an immune complex, rather than IgG (47). Apparently, tolerance to IgG exists at the T cell level, while RF precursor B cells are common. The RF precursor B cells will proliferate in response to help provided by T lymphocytes recognizing exogenous antigens bound to IgG. Alternatively, nonspecific T cell help, such as occurs during a graft vs. host response, or after exposure to certain bacterial toxins, can trigger the RF precursors to divide.

The eventual appearance of high-titer IgM-RF and IgG-RF may require repeated exposure to antigens that induce formation of abundant immune complexes that can elicit a vigorous T cell response. Under these conditions, the relatively uncommon RF-secreting B cells, which utilize many different immunoglobulin genes, would expand and mutate. This process would be expected to occur more frequently in people with deletions of one or more of the physiologic RF genes associated with antigen-presenting B cells in the mantle zone.

Our recent research has focused on the immune response to two microorganisms that chronically infect most people, the Epstein-Barr virus and *Escherichia coli* (48, 49). Both organisms express antigens (the gp110 protein of EBV and the DNA J heat shock protein of some *E. coli* strains) that contain a section of the rheumatoid arthritis disease susceptibility sequence in the HLA-DR4 molecule (48, 49). One can readily conceive of a scenario in which epitope sharing between self and nonself impairs the development of effective cytotoxic immune responses to these microorganisms, such that immune complexes are produced repeatedly. The repeated loading of RF precursors with peptide fragments that mimic HLA-DR4 sequences could eventually stimulate some helper T cells that are restricted by (and hence can bind to) autologous class II molecules, at least with low affinity. Because the efficiency of T-B interaction is a function of affinity times valence, the focusing of self-peptides by antigen-presenting RF precursors may be a critical factor in the induction of autoimmune responses against a variety of autoantigens in the joints. It must be remembered that somatic mutation of antibody V genes permanently alters the immune system. Once RF class switching, clonal expansion, and affinity maturation reaches a critical threshold, it can become self-sustaining, because intermittent exposure to small amounts of any antigen-antibody complex would progressively boost RF synthesis.

Prospects for Therapy

If the associations between polymorphisms in the RF heavy chain V region genes and autoimmune disease are confirmed, and is additive to the known HLA associations, susceptible patients could be identified before disease onset, with greater predictability than is now possible. Such a high-risk group would be particularly suitable for epidemiologic and interventional efforts aimed at determining how exposure to a common bacteria or virus can trigger sustained autoantibody production and joint disease. In patients with the RF-associated lymphoproliferative diseases, prospects for therapy are closer at hand. Considering that CLL cells have a low growth fraction, and often express RF-associated cross-reactive idiotypes, they are potential targets for idiotype-directed passive or active immunotherapy. With the available DNA probes and antiidiotype antibodies, one can quickly determine gene usage and heterogeneity in a blood or bone marrow sample. As such, the characterization of the genes encoding RF offers prospects for the diagnosis and treatment of both autoimmune and lymphoproliferative diseases.

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