Clonal expansion is a characteristic feature of the B-cell repertoire of patients with rheumatoid arthritis

ABSTRACT

The present study was designed to analyze the level of B-cell clonal diversity in patients with rheumatoid arthritis by using HCDR3 (third complementarity determining region of the rearranged heavy chain variable region gene) length as a marker. A modified immunoglobulin VH gene fingerprinting method using either genomic DNA or complementary (c)DNA derived from B cells of the peripheral blood, synovial fluid, and tissues of several rheumatoid arthritis patients was employed. These assays permitted the detection and distinction of numerically expanded B-cell clones from activated but not numerically expanded B-cell clones. The present data suggest that B-cell clonal expansion is a common and characteristic feature of rheumatoid arthritis and that it occurs with increasing frequency from the blood to the synovial compartments, resulting in a narrowing of the clonal repertoire at the synovial level. These clonal expansions can involve resting, apparently memory B cells, as well as activated B cells. Furthermore, some of these individual expansions can persist over extended periods of time. These findings support the hypothesis that a chronic ongoing (auto)immune reaction is operative in rheumatoid arthritis and that this reaction, at least at the B-cell level, may be unique to each individual joint. A determination of the targets of these autoimmune reactions may provide valuable clues to help understand the immunopathogenesis of this disease.

INTRODUCTION

Introduction Rheumatoid arthritis is a chronic debilitating autoimmune disease of unknown etiology. Although the disease is characterized by synovitis of the joints, tendon sheaths, and bursae, manifestations that do not involve the synovium are not infrequent. These articular and systemic manifestations appear to be mediated by immunologic processes. The hallmarks of the synovial abnormalities in rheumatoid arthritis are synovial lining cell proliferation, neoangiogenesis, and inflammatory cell infiltration involving the myeloid, macrophage, and lymphoid lineages. There has been considerable controversy regarding the relative importance of the types of cells and their products involved in the inflammatory processes of rheumatoid arthritis. Nevertheless, it seems likely that all of these cell types participate to some degree in disease pathogenesis. Evidence in support of T-cell involvement in rheumatoid arthritis involves the description of restricted subsets of T cells in the blood and synovial tissue that either express or lack certain surface membrane proteins or that express a limited set of antigen receptors. For example, clonal amplifications of CD8+ CD57+ T cells are frequently found in the T-cell repertoire of rheumatoid arthritis patients. Furthermore, expanded clones of CD4+ CD28- T cells exist in the blood and synovial compartments of such patients and these T cells appear to be autoreactive. Finally, the T-cell receptors for antigen expressed by these and other T-cell subsets frequently display a bias in favor of receptors utilizing certain Vβ genes. In contrast to the extensive studies of the clonal distribution of T cells in rheumatoid arthritis, much less is known about the level of B-cell diversity in this disease. Previous studies, however, are consistent with the interpretation that the B-cell repertoire is also restricted. For example, flow cytometric analyses of circulating B cells suggested that oligoclonality exists, and cell culture experiments demonstrated that synovial tissue explants spontaneously secrete immunoglobulins of restricted heterogeneity as defined by immunoglobulin

(Ig)G subclass, isoelectric focusing, and idiotype expression. More recent molecular analyses of the immunoglobulin genes expressed by B cells in the synovial tissue of rheumatoid arthritis patients support these notions. These findings are important because they suggest that, at the B- and T-cell levels, an ongoing immune reaction is occurring that is directed at restricted sets of (auto)antigens. The present study was designed to analyze further the level of clonal diversity in rheumatoid arthritis B cells by using the length of the third complementarity determining region (CDR3) of the rearranged heavy (H) chain variable region (V) gene as a marker (herein referred to as HCDR3). A modification of the immunoglobulin VH gene fingerprinting method that has been used to analyze the diversity of B cells and T cells in several clinical settings was used to address this issue. The present data suggest that B-cell clonal expansion is a common and characteristic feature of rheumatoid arthritis, that it involves both resting and activated cells, and that it can persist over extended periods of time. These findings support the idea that a chronic (auto)immune reaction is operative in rheumatoid arthritis.

CONCLUSION

The present data indicate that clonal expansion is a common occurrence in the B-cell repertoire of rheumatoid arthritis patients. These expansions involve both resting memory B cells and activated B cells, some of which are derived from the memory B-cell compartment. Because the extent of these clonal expansions increases from the blood to the synovial compartment, this progressive narrowing in diversity implies that antigens located in the synovia are responsible for these antigen-receptor biases. In support of this hypothesis are the observations that some of these clonal expansions are joint specific. Because identical clones are rarely found in two different joints, however, these immune reactions are probably unique to each individual joint. Furthermore, because it is unlikely that each joint would harbor a different foreign antigen, these B cells are most likely reacting with autoantigens generated locally, possibly by local tissue breakdown. Recent studies have demonstrated that the synovial tissue of rheumatoid arthritis patients can develop lymphoid aggregates that have the cellular components of an ectopic germinal center and that can sustain B-cell clonal expansion and diversification. It is likely that the B cells that mature in these 'pseudogerminal centers' and those that we have identified in the present studies are responding to specific (auto)antigens. Therefore, the identification of the antigenic reactivities of these B cells, and in particular those B cells within the memory compartment that have presumably traversed the pseudogerminal centers and undergone (auto)antigen and T cell selection and rescue, may provide important clues to the role of B lymphocytes and their immunoglobulin molecules in the immunopathogenesis of rheumatoid arthritis.