Feedback regulation of antibody production: a role in rheumatoid arthritis?

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Mechanisms controlling antibody synthesis in rheumatoid arthritis (RA) are defective. This is clear not only from the observations that hypergammaglobulinaemia and autoantibody formation are common findings in RA, but also from the joint pathology where numerous plasma cells are actively synthesising immunoglobulin.¹ Such observations have led to intensive investigations of the pathways that regulate antibody synthesis. Most of these have centred on T cell function and have shown that suppressor cell activity in RA is impaired, especially in the joint.²⁻⁶ Another mechanism exists, however, which is also important in controlling the antibody response—namely, Fc mediated negative feedback suppression. This process is often ignored in investigative studies of immunoregulation but should not be overlooked as defects here may adversely affect other control mechanisms. Idiotype-anti-idiotypic interactions are recognised as an important part of the immunoregulatory circuit and there is evidence that such control may be mediated through feedback suppression.⁷ This review considers the mechanisms underlying feedback inhibition and its possible role in the pathogenesis of RA. It should be appreciated that not all Fc mediated effects are suppressive. Thus complexes containing both IgM⁸ and IgG antibodies⁹ may enhance immune responses under certain conditions, and Weigle's group has reported extensively on a stimulatory fragment derived from human IgG-Fc.¹⁰⁻¹²

That antibody can regulate its own production has been known for nearly 100 years. Workers in the late 19th and early 20th centuries noted that preformed antigen-antibody complexes could either enhance or suppress the humoral response. Subsequent studies showed that passively administered antibody was able to suppress specifically the response to a given antigen.¹³⁻¹⁵ This was thought to occur through the masking of antigenic determinants by antibody—a concept supported by the observations that higher affinity antibodies were more effective than those of lower affinity¹⁶ and that $F(ab')_2$ was reported to be equipotent with the whole IgG molecule.¹⁷ Other data emerged, however, which suggested a different mechanism. Uhr and Bauman showed that antibody injected five days after immunisation was still able to suppress the immune response, suggesting that a feedback mechanism was operating.¹⁸ In addition, Sinclair reported that $F(ab')_2$ was 1000-fold less effective than intact IgG in causing suppression and that this difference lay in the presence of the Fc portion.¹⁹ These conflicting data were united by Hoffman and Kappler,²⁰ who postulated that antibody

mediated suppression operated at two levels: antigen masking did occur at high concentrations of antibody, but at low levels, where this was ineffective, an Fc dependent mechanism came into play.

Exactly how this suppression occurs and the Fc receptor involved are unclear. Three distinct types of Fc receptors have been identified on human leucocytes,²¹ with Fc receptor II predominating on B lymphocytes. Two mechanisms for Fc mediated suppression have been proposed: one suggests that this occurs by interference with T-B cell cooperation²² and the other advocates direct B cell blockade.²³ Although there is evidence to support both these mechanisms, many of the recent reports have concentrated on the latter pathway. In 1971 Sinclair and Chan proposed a tripartite inactivation model to show how B cell blockade might occur.²⁴ It was suggested that immune complexes were able to bind to B lymphocytes via both the antigen receptors (surface immunoglobulin) and Fc receptors. Cross linking of these two entities was thought to inactivate the cell. Subsequent investigators demonstrated this using various Fc receptor ligands.²⁵ The lymphocytes are thought to be diverted from plasma cell formation to memory cell generation.²³ Indeed it has been recognised that immune complexes, although effectively suppressing the primary response, are highly efficient in allowing priming of lymphocytes in preparation of the secondary response.²⁶ An alternative view invoking a factor derived from B cells exposed to IgG aggregates in the suppressive mechanism has also been reported.²⁷

The exact nature of the negative signal delivered by immune complexes is not yet known. Antigen receptors on B cells belong to a class of Ca^{2+} mobilising receptors.²⁸ Ligand-receptor interaction causes the activation of a membrane phosphoinositol biphosphate diesterase through a G protein,^{29,30} leading to hydrolysis of membrane phosphoinositol biphosphate to generate second messengers inositol trisphosphate and diacylglycerol.³¹⁻³³ The former causes release of Ca^{2+} ions from intracellular stores,³⁴ whereas the latter activates the Ca^{2+} dependent protein kinase C³⁵ which causes phosphorylation of proteins and hence cell activation. Using antibodies to IgM, Bijsterbosch and Klaus found that cross linking of Fc receptors and surface immunoglobulin on murine B cells inhibits cell activation by preventing second messenger generation.³⁶ This is thought to occur through the uncoupling of antigen receptors from an as yet undefined G protein, Gp.³⁷

There is evidence to suggest that T cell

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factors may interfere with feedback inhibition of antibody synthesis. Earlier investigations showed that the presence of factors that provide T cell 'help' (tumour necrosis serum) was able to prevent suppression.¹⁹ There is evidence to show that the cytokine T cell replacing factor can bind to Fc receptors.³⁸ It was suggested that the outcome of B cell activation depends on competition between T cell replacing factor and immune complexes at the Fc receptor site.²² More recently, interleukin 4/B cell stimulating factor 1 has been shown to reverse feedback suppression in a small number of murine B cells, whereas B cell growth factor II, which is synonymous with T cell replacing factor,³⁹ had no effect.⁴⁰ That T cells can affect feedback inhibition is also indicated by Sinclair and Panoskaltis,⁴¹ who found that blocking of Fc binding by antibody to Fc dramatically reduced the number of T cells required to generate an immune response to a T cell dependent antigen. Thus part of the T cell 'help' generated during a normal immune response is apparently needed to overcome the downregulated state of B cells.

Investigations of feedback suppression in patients with rheumatoid arthritis have been rather limited. Patients with rheumatoid disease are reported to have increased⁴²⁻⁴³ or normal levels of Fc receptor expression.⁴⁴ Using a modified rosette assay, we have shown that the increased levels of Fc receptor expression may in part be due to significantly raised numbers of cells expressing receptors for the CH2 region of rabbit IgG (Facb-R+ cells).⁴⁵ These bear neither T nor B cell markers but do possess certain monocyte related antigens and exhibit major histocompatibility complex class II antigens.⁴⁶ Similar cells have been described as OKM1+ granular lymphocytes by Cooper and colleagues.⁴⁷ Facb-R+ cells have been shown to be involved in feedback suppression using both murine⁴⁸ and human cell systems,⁴⁹ and the increase in Facb-R+ cells in rheumatoid patients might therefore be thought to reflect the attempt of the immune system to control B cell hyperactivity. When feedback suppression of *in vitro* IgG synthesis was examined in these subjects, however, it was found to be significantly impaired compared with that in healthy controls.⁴⁹ Patients with ankylosing spondylitis or osteoarthritis showed normal feedback suppression of IgG production, as did patients with early (less than two years) RA.⁵⁰ Other workers have also shown impaired Fc receptor dependent regulation of B cells in RA.⁵¹ Two main conclusions thus emerge from these data: firstly, Fc receptor expression and the ability to suppress through feedback inhibition are not directly related and, secondly, a process associated with disease chronicity rather than the disease itself is involved in the impaired feedback suppression noted in established RA. Whatever the mechanism, it is clear that Fc receptor signalling is impaired in RA as neutrophils from rheumatoid subjects show reduced Ca²⁺ ion fluxes when triggered by coligation of Fc receptor with antibodies to either Fc receptor II or Fc receptor III.⁵² It may be that in a chronically stimulated immune system B lymphocytes become refractory to negative

signals delivered through the Fc receptors. For example, it has been shown that Fc receptor mediated suppression of B cell activity is impaired in NZB mice where autoimmune and B cell hyperactivity occur spontaneously.⁵³

In vivo, the efficiency of feedback suppression will depend not only on Fc receptors but also on the properties and availability of antibody. In RA agalactosyl IgG has been found in high concentrations in patients with active disease.⁵⁴ These IgG molecules cannot bind to Fc receptors⁵⁵⁻⁵⁶ and therefore do not participate in feedback suppression.⁵⁷ It is of considerable interest that a significantly higher proportion of patients with early synovitis with agalactosyl IgG were subsequently found to develop RA compared with those with normal IgG (Young *et al*, unpublished data). It is likely that a defect in feedback suppression in established RA may be further exaggerated *in vivo* by the presence of IgM rheumatoid factor. This autoantibody is produced in response to normal immunisation⁵⁸⁻⁵⁹ and may, it has been suggested, have a role in preventing feedback suppression, thus allowing maximal development of an immune response.⁶⁰ In RA persistently high levels of rheumatoid factor may restrict the amount of antibody available for feedback suppression.

In conclusion, feedback inhibition of antibody production in patients with established RA is depressed. This is in part related to the impaired function of regulatory cells, possibly reflecting poor Fc receptor signal transduction. Rheumatoid IgG, however, may be less able to deliver an effective negative signal owing to its partially deglycosylated state. Other factors associated with chronic rheumatoid inflammation may also disrupt feedback suppression through competition for the relevant binding sites. These include rheumatoid factor interacting with IgG-Fc and cytokines binding to Fc receptors. Clearly, much more needs to be done to evaluate the significance of feedback suppression in the overall process of immunoregulation and its dysfunction in rheumatoid disease.

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