Ia antigens and F_C receptors

from Robert S. Kerbel

IDEAS come and go, certainly, but the rapidity with which they occasionally do so can leave one a little breathless. Barely has the latest, most fashionable theory been digested before it is threatened with obsolescence.

Take the case of Ia antigens and F_c receptors: the former are alloantigens determined by the I (immune response) region of the mouse major histocompatibility (H-2) complex while the latter are membrane-associated receptors which recognise the F_c portion of certain immunoglobulin molecules. F_c receptors are found on a wide variety of cells including B lymphocytes, activated T cells, macrophages, neutrophils and eosinophils. The function of both these entities is unclear and currently the subject of interest but they have been implicated in a wide spectrum of immune phenomena including genetic control of immune responses, mechanisms of cell cooperation, and regulation of immune responses. It was therefore a finding of considerable potential importance when Dickler and Sachs (*J. exp. Med.*, **140**, 779; 1974) reported evidence for an identity or close association of the F_c receptor and Ia antigens on B lymphocytes.

The evidence consisted primarily of inhibition experiments in which the uptake of whole heat-aggregated immunoglobulin (Agg-Ig) molecules by mouse B cells—one way of apparently detecting F_c receptors—could be significantly inhibited by preincubating the cells with specific anti-Ia sera, but not with iso-antisera which reacted with the antigens determined by the K or D regions of the H-2 complex, nor with a heterologous anti-mouse Ig serum which reacted with Ig-bearing mouse B cells. Thus, there seemed to be some sort of unique relationship between alloantigens controlled by the I region of the H2 complex and the F_c receptor.

This conclusion has now been challenged by the findings reported by Schirrmacher, Halloran, and David (*J. exp. Med.*, **141**, 1201; 1975). These investigators essentially repeated Dickler and Sach's experiments, but used two alternative assays to detect F_c receptor-bearing cells. One of these, called F_c or EA rosette formation, detects F_c-receptor bearing cells by virtue of the cells forming clusters or 'rosettes' with IgG antibody-coated erythrocytes. When Schirrmacher *et al.* preincubated their B cells with anti-Ia sera, F_c rosette formation was markedly diminished, in agreement with Dickler and Sachs. But when the same procedure was repeated using a variety of other antisera, all of which react with B cells, including anti-

Ly4.2, anti-MBLA, and anti-Ig, inhibition of rosette formation also occurred. Anti-T cell sera did not effect such inhibition. Furthermore, the authors cited further experiments in which anti-H2D or anti-H2K sera caused significant inhibition. The authors also showed that F(ab)₂ fragments of some of the various antisera preparations possessed similar inhibiting capacities to the intact molecules, which proved that the observed inhibition using intact antisera was not due to the formation of third party immune complexes pre-empting F_c receptors, as been observed in other assay systems detecting F_c receptors (Halloran and Festenstein, *Nature*, **250**, 52; 1974; Basten *et al.*, *J. exp. Med.*, **141**, 547; 1975).

On the face of it, these results certainly provide no support for the view that a unique association exists between Ia antigens and F_c receptors, although, in fairness, they do not formally disprove the notion either. For example, if it can be shown that 'capping' of Ia antigens also leads to co-capping of F_c receptors whereas capping of Ly4.2 or MBLA antigens does not, then it could still be argued that a unique association between Ia antigens and F_c receptors does indeed exist.

For the moment, the obvious question is: why the differences in results? An equally obvious answer would be to implicate the different assay systems used. There have been a number of findings lately which seem to make it clear that the F_c rosette test and the Agg-Ig binding assay may not be detecting the same receptor, or the same cell(s). Indeed Froland, Natvig, and Michaelsen (*Scand. J. Immun.*, **3**, 375; 1974) have recently claimed that the binding of aggregated IgG by human B lymphocytes can occur independent of F_c receptors. Conversely EA rosette formation required F_c receptors, but—at least in their experiments—the rosette-forming cells did not seem to be classical Ig-bearing B cells.

With regard to the conflicting results obtained when using these two different assay systems, it should also be noted that Schirrmacher *et al.* used an additional, functional, test system to detect F_c receptors and, once again, found no evidence for a unique association between Ia antigens and F_c receptors. The system involves the use of antibody-coated chicken erythrocytes as target cells in a cytotoxic assay in which normal spleen cells attack the target cells by virtue of F_c receptors on the killer cells (K cells) interacting with the membrane-bound antibody molecules. When antibody molecules with specificity for the K cell or any other cell found in normal spleen, are added to the system, inhibition of cytotoxicity is observed as a result of pre-emption

of the F_c receptor on the K cell by the antibody-coated spleen cells (Halloran, Schirrmacher, and Festenstein, *J. exp. Med.*, **140**, 1348; 1974). This assay, called 'cytotoxicity inhibition assay' or a timely CIA for short (none of the authors is American), demonstrated that F_c receptor-bearing K cell activity was inhibited by all of the sera mentioned above, including anti-T cell sera. More importantly F(ab')₂ fragments of the antisera—including anti-Ia—did not cause any inhibition. Once again, if the F_c receptor and Ia antigens are identical or closely associated, one might have expected some inhibition of K cell activity by the addition of F(ab')₂ fragment of the anti-Ia serum.

It therefore seems prudent at this time to exercise restraint before making any categorical assumptions about the association of F_c receptors and Ia antigens.

Organisation and disorder in membranes

from J. C. Metcalfe

SINCE Gorter and Grendel introduced the bilayer concept in 1925, the many speculative models of membrane structure have not led to any precise insight into how structure is related to function. At present, the fluid-mosaic model, popularised by Singer and Nicholson, has the merit of emphasising the balance between the structural organisation and the fluid disorder of membrane lipids and proteins, which are both established on an experimental basis. In different membranes this balance ranges from the extremely fluid disk membranes of rod outer segments, in which rhodopsin and the lipids diffuse laterally at rates of up to a micrometre a second, to the very rigid two-dimensional latttice of 'bacteriorhodopsin' which is the only protein in the purple membrane fragments of halobacteria. This contrast is especially striking because both proteins use the same retinal chromophore to transform light into a biochemical signal.

The IUB-IUPAC Symposium in Tehran (5-7 May) on "The Structural Basis of Membrane Function" provided some striking examples of the underlying tension between structural order and fluidity in modulating the many biochemical functions which can coexist in a single membrane. The purple membrane, which combines extreme order and simplicity of composition, provides an exceptional opportunity for a complete structural and functional analysis. The bacteriorhodopsin functions as a light-driven proton pump and W. Stoeckenius (University of California) reported that at least four inter-