Immunoglobulin Profiles Provide New Insights into Infectious Diseases

ANN SCHLUEDERBERG, Sc.D.

Division of Research Grants, National Institutes of Health, Bethesda, Maryland

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New technologies are being developed which will facilitate measurement of IgG subclass responses to disease and vaccination. To illustrate the potential benefit of determining antibody subclass profiles, special features of the less abundant subclasses are discussed in relation to specific infectious disease problems.

We are tooling up for an exciting period in infectious disease immunology. As more and more monoclonal antibodies become available, we will be able to look at antibody responses in terms of both antibody subclass and individual microbial antigenic specificity. Just as determination of antibody class is informative in diagnosis [1], vaccine evaluation [2,3], and epidemiology [4], determination of antibody subclass is sure to provide welcome explanations for unusual host reactions and immunopathogenesis.

A good example of the latter is Berger’s disease, which is a common type of glomerulonephritis with onset of symptoms often coinciding with upper-respiratory tract infection or gastroenteritis. The finding of a high proportion of IgA1 in glomerular deposits in this disease supports the idea that renal pathology is caused by deposition of immune complexes of IgA derived from plasma cells associated with mucosal surfaces. This is in contrast to the primarily IgA1 renal deposits in lupus erythematosus [5].

IgG subclass determination promises to be particularly informative, because IgG subclasses show important biological differences (Table 1). The time at which adult serum levels are reached varies markedly, and we can expect that age-associated variation in disease severity will become more explicable in these terms. This is well illustrated by the severity of encapsulated bacterial infections in young children. IgG antibody responses to polysaccharide capsular antigens are restricted to IgG2, which is the last subclass to appear in the infant and the last to reach adult levels [25,26]. As expected, genetic deficiency in IgG3 has been reported to be associated with severe and recurrent infections with these agents [27].

Examples of such restriction and consequent disease effects are not yet documented for viruses, but subclass restriction may provide the explanation for a well-known but unexplained observation. The complement-fixing (CF) antibody responses to certain antigens of a number of different viruses—notably the togaviruses—share a characteristic post-immunization time course: late appearance and early decline. Since IgG3 antibodies have a strong CF capacity and a catabolic rate which is uniquely short, we may find that these CF antibodies are restricted to
TABLE 1
Human IgG Subclass Characteristics

|                     | IgG1 | IgG2 | IgG3 | IgG4 | Ref. |
|---------------------|------|------|------|------|------|
| Physiologic:        |      |      |      |      |      |
| Cross placenta      | +    | ±    | +    | +    | [6,7]|
| Physiological half-life (d) | 21   | 21   | 7    | 21   | [8]  |
| Age when adult levels attained | 8 mo | 12 y | 3 mo | 50% 2 y | [9,10] |
| Relative concentration (%) | 66 | 23 | 7 | 4 | [11] |
| Biologic:           |      |      |      |      |      |
| Complement fixation | +    | +    | +    | +    | [12] |
| Reversed PCA, guinea pig | +  | -   | +    | +    | [13,14] |
| Attach to monocytes | +    | -    | +    | -    | [15] |
| Attach to lymphocytes | +  | +    | +    | -    | [16] |
| Attach to mast cells, subhuman primates | -  | -   | -    | +    | [17] |
| Associated immediate hypersensitivity | -   | -   | -    | +    | [18,19] |
| React rheumatoid factor | +  | +   | -    | +    | [20] |
| Biophysical-biochemical: |      |      |      |      |      |
| Bind to Protein A   | +    | +    | -    | +    | [21] |
| Papain labile (− cysteine) | +  | -   | +    | -    | [22] |
| Papain labile (+ cysteine) | -  | +   | +    | -    | [22] |
| Electrophoretic mobility | slow | fast | medium | fast | [23] |
| Isoelectric focusing | broad > 8 | 6-8 | > 8 | 6 | [24] |

the IgG3 subclass. If so, the failure of some persons to mount measurable levels of CF antibody following rubella might reflect their allotype [28]. For example, total IgG3 levels are about twice as high in individuals homozygous for Gm(5) as in those homozygous for Gm(21) [29].

An important area in virology where IgG subclass serum profiles may provide needed answers is the study of serious reactions to virus challenge in the partially immune host [30,31]. IgG4 seems likely to play an important role, since it has been associated with hypersensitivity reactions of the immediate type, and in at least one case of severe anaphylactic reaction, appeared to be the only immunoglobulin involved [32]. The maintenance of an appropriate balance in specific class and subclass antibody levels may be critical in determination of immunopathological outcome. We can easily imagine how this balance might be disturbed in the partially immune host, but we cannot begin to understand the implications until more is learned about the individual time courses and feedback restrictions in primary and secondary antibody responses. In the absence of a clear understanding of these variables and their interrelationships, it is little wonder that mechanisms of antibody-mediated pathology have defied definition. In this regard, it will be of interest to learn how IgG subclasses and allotype figure in the pathogenesis of dengue hemorrhagic fever—a disease for which none of the proposed mechanistic theories has proved to be entirely satisfying [33–35].

In pursuit of these and related questions, monoclonal antibodies will be of enormous help. The extreme differences noted between these subclasses should also signal caution in the interpretation of data derived with an IgG monoclonal reagent, for its activity will depend on the subclass. As an example, a human IgG4—or mouse IgG1—monoclonal antibody specific for a viral "CF antigen" might go unrecognized
if tested only by complement fixation. Moreover, reactivity attributed to subclass may, in fact, be associated with allotypic or other determinants.

We are now in an era when new serologic tools often are adopted because of ease of execution (ELISA) or increase in sensitivity (RIA), without regard to the loss of individual antigenic specificity associated with classical tests such as inhibition of hemagglutination, inhibition of hemolysis, and neutralization. Thus, “old-fashioned” tests permit discrimination between antigenic specificities even with relatively crude antigens, whereas the “new fangled” tests do not. Fortunately, scientific curiosity and commercial interests assure that both sensitivity and specificity will eventually surpass our dreams with the provision of monoclonal antibodies specific for individual microbial antigens and for individual human immunoglobulin subclasses. When these reagents are intelligently and fully exploited, we can expect clarification of earlier observations and many exciting insights.

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