Immunology 101: Understanding Antibody Class-Switch

By Terry O. Harville, MD, PhD

LAST MONTH’S COLUMN ended with a discussion of the somatic (or acquired) mutation of immunoglobulin genes to produce an antibody that can have a stronger affinity for an antigen and, therefore, stronger protection against a pathogen. We also discussed that the initial antibody, IgM, is typically “switched” to IgG production. All of this occurs to increase the affinity and specificity of the antibody.

The Process of “Class-Switch”

The process of changing from IgM production to IgG production (and also to IgA and IgE production) is called “class-switch.” This occurs based on the linear arrangement of the immunoglobulin heavy chain gene components on chromosome 14. Although we tend to speak only of IgG, there actually are four subclasses of immunoglobulin G: IgG1, IgG2, IgG3 and IgG4. Additionally, there are two subclasses of IgA: IgA1 and IgA2. IgG proteins (as a result of the gene positions and arrangements) can be broadly apportioned into two parts — 1) the “variable” (V) region and 2) the “constant” (C) region — which when brought together make the functional antibody. The V region arises from specific gene recombination events (to be discussed in detail later). Each new V region defines the antibody specificity, of which many millions can be generated, but our bodies ultimately select 15 million or so to be our antibody repertoire.

The immunoglobulin heavy chain genes reside on chromosome 14 in this order: variable (V) genes — IgM constant gene — IgD constant gene — IgG3 constant gene — IgG1 constant gene — IgA1 constant gene — IgG2 constant gene — IgG4 constant gene — IgE constant gene — IgA2 constant gene. During B lymphocyte development, the recombined V gene will be transcribed with the IgM constant gene or IgD constant gene and will be expressed as IgM or IgD proteins, respectively, on the surface of the developing B lymphocyte. Subsequently, IgM will be secreted into the blood. If a specific antigen can be recognized by this B lymphocyte and its specific IgM antibody, and T lymphocyte stimulation occurs, then the B lymphocyte can be stimulated. With stimulation, and depending on the type of antigen being responded to, the DNA between the V gene and a specific C gene will be removed, and class-switch will occur.

For example, tetanus toxoid protein antigen tends to elicit an IgG1 antibody response. After the B lymphocyte has received appropriate stimulation, the intervening DNA between the tetanus toxoid-responsive V region gene and IgG1 C region gene (IgM constant gene — IgD constant gene — IgG3 constant gene) is removed from chromosome 14, bringing about class-switch. Another example is: If an IgE antibody is to be produced, the intervening DNA containing the IgM constant gene — IgD constant gene — IgG3 constant gene — IgG1 constant gene — IgA1 constant gene — IgG2 constant gene — IgG4 constant gene will be removed, again bringing about class-switch to IgE production. After class-switch, the process cannot go backward. In other words, if there has been a switch to IgE production, there can never be a return back to IgG1, IgG2, IgG3, IgG4 or IgA1 antibody production.

Antibody Classes and Subclasses

At this point, it should be recognized that we have the capacity to produce nine different classes and subclasses of antibodies: IgM, IgD, IgG1, IgG2, IgG3, IgG4, IgA1, IgA2 and IgE. Each has a specific role for which it is best suited.

For instance, IgD has an important role during B lymphocyte development. And, it may have a role in subsequent activation of B lymphocytes, but not a major antigen recognition role. Because IgD is typically not found in the bloodstream, deficiency of IgD is not recognized as causing adversity (immunodeficiency). Alternatively, elevation of IgD in the blood is found in the autoimmune disorder known as hyper-IgD syndrome (HIDS), which is a periodic fever syndrome. These patients may have bouts of unexplained fevers and rashes at periodic intervals, severe mouth ulcers, abdominal pain, joint and muscle discomfort. HIDS patients don’t, however, experience recurrent infections.

Next month, we will continue defining the roles of the specific classes and subclasses of immunoglobulin.

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Editor’s Note: This Immunology 101 column, introduced in the April-May 2010 issue of IG Living, is intended to be a basic course in immunology. Each column builds upon the information introduced in each previous column. To read the columns in the order they have been published, go to the past magazine’s issue archives at www.igliving.com.