Memory B Cells and Antibody Function

By Ricardo Sorensen, MD, and Lily Leiva, PhD

Editor’s Note: This was originally an Ask Kris question that was submitted to Ricardo Sorensen, MD, professor of pediatrics, department chairman at Louisiana State University, and Lily Leiva, PhD, associate professor and director of immunology laboratory at LSU. The first part reflects the original question, “What is the role of memory B cells in the immune system and immune deficiencies?” After answering the initial question, Dr. Sorensen shared more insight on current research, saying, “This is a rapidly evolving field, and I think patients and MDs need to be aware of the potential implication of having low memory B cells.”

The Role of Memory B Cells

Deficiencies in antibodies that fight common bacteria and viral infections are frequently found in patients who have recurrent or severe infections. These deficiencies are diagnosed by measuring immunoglobulins (IgM, IgG, IgA) and specific antibodies directed against components of commonly used vaccines like tetanus, diphtheria and also pneumococcal vaccines (Prevnar and Pneumovax). We and some other immunologists also measure IgG subclasses, although others express concerns about the value of IgG subclass determinations.

Immunoglobulins and the specific antibodies that are included in each of the immunoglobulins are produced by plasma cells that reside mostly in the bone marrow and intestinal lymphoid tissue. Plasma cells are the most differentiated forms of the B lymphocyte lineage. B cells normally mature from precursor cells without needing any exposure to bacterial antigens to mature.

When B cells encounter bacterial and other proteins and sugars that they recognize as foreign materials, they develop in two directions: Some become plasma cells (immunoglobulin and specific antibodies), and others become memory B cells that recognize the same foreign substances that started the reaction to begin with. These memory B cells have been the subject of intense research in recent years.

Clinical Implications of Memory B Cell Testing

For many years, testing of antibody-mediated immunity involved measuring the plasma cell products, immunoglobulins, specific antibodies and, in some cases, measuring the number of mature B cells in circulation. Very low circulating immunoglobulin concentrations plus the absence of circulating mature B cells (CD20 and CD19 surface molecule positive cells) defined a severe immunoglobulin deficiency, agammaglobulinemia. Other forms of immunoglobulin deficiency have normal circulating mature B lymphocytes. This means that when immunoglobulins or specific antibodies are produced normally, something is wrong with the ability of B cells to become antibody-producing cells.

Recently, improved and easier ways to recognize and count several types of memory B cells have become available in immunology research laboratories. Exact definitions of what are normal or abnormal numbers of these various types of memory B cells are still lacking. The influences of age, gender, patient population studied, plus laboratory to laboratory variations still need to be better defined. However, it has become clear that abnormalities in memory B cells are part of this picture for many patients. Patients with low immunoglobulins may have normal mature B cells, such as in common variable immunodeficiency (CVID), in the more controversial IgG subclass deficiencies, and also in specific antibody deficiencies that have normal immunoglobulins and IgG subclass concentrations. Most remarkably, we have recently identified patients who also appear to have normal specific antibodies to pneumococcal polysaccharides but who continue to be sick. Based on observations made by basic immunologists, we are beginning to understand that some individuals may have immunoglobulins and antibodies as presently measured, but their antibodies do not function properly. While it would be ideal to have assays that measure not only antibody concentrations but also their function, assays that measure function are difficult to perform and not clinically standardized or available for routine testing. The measurement of memory B cells may become a surrogate test for this type of abnormality. Active research in this area is needed to further study the clinical implications of memory B cell abnormalities. If eventually accepted as a marker for deficiencies in antibody-mediated immunity, abnormalities in memory B cells could open the door to treatment for some patients who presently do not fit into any accepted diagnostic and treatment category.

B Cell Subsets

Dr. Sorensen’s current research into memory B cells focuses on a specific subset: class-switched memory B cells (the graphs’ upper-left quadrants). In healthy individuals, this type of B cell accounts for 9%–19% of all memory B cells. In some patients, however, as the graph on the right shows, class-switched memory B cells are exceedingly sparse. In the future, being able to assess patients’ class-switched memory B cells may help ascertain their clinical prognosis more specifically, for example, by determining whether they will be more prone to respiratory infections.