Immune Polyreactivity

When a person has highly elevated antibodies against all, or nearly all, antigens on an antibody test panel, the antibodies are referred to as polyreactive antibodies. Polyreactive antibodies (PAbs) are antibodies that are produced against a particular antigen or antigens, but can bind to a variety of different and structurally unrelated self- (Fc fragment of IgG, insulin, thyroglobulin, ssDNA) and non-self- (bacteria, viruses) antigens with simple (haptens) or complex (carbohydrates, proteins, nucleic acids, lipids) structure.[1] Because of their flexibility, PAbs can be a normal product of the immune system or they may become pathogenic, depending on conditions.[2]

PAbs were discovered in the early 1980s. Research ensued to elucidate the function of these special antibodies. It was concluded that PAbs are cleared from the circulation substantially faster than monoreactive antibodies,[1] which explains why many polyreactive patients live inflammation-free, healthy lives.

In health, polyreactivity of immune receptors magnifies the antigen detection power of the immune system and endows the system with the ability to exert regulation of its own functions.[2] These circulating PAbs are low-affinity antibodies that do not damage self-tissue.[3] If conditions remain in this state, a person producing PAbs will remain healthy.

On the other hand, the presence of PAbs has been associated with different autoimmune, inflammatory, and infectious diseases. PAbs can break immune tolerance and cause the formation of immune complexes as seen in autoimmunity; PAbs can stimulate cells as seen in allergy; PAbs can even contribute to malignancy by perpetual malignant cell stimulation.[2] It is still not clear whether, or not, PAbs play a direct role in immune disorders leading to disease. In cases of infection, PAbs can assist the cell infiltration of certain pathogens,[2] and low-affinity PAbs have been shown to switch to high-affinity in HIV patients.[4]

Not all polyreactive patients have health problems. However, they are at greater risk for developing health problems, if the polyreactive patient's body encounters a traumatic event. Acute physical (infection, car accident) or emotional (death of loved one) stressors can switch natural polyreactivity to a state of high-affinity binding. For others, the first immune response can be low-affinity PAbs, later followed by high-affinity, in pathogenesis progression.[5]

Certain conditions can cause a person to produce PAbs.

- Pathogens, including periodontal pathogens, which can result in multiple positives on Array 14.
- Microbe involved in biofilm formation.
- Bacterial toxins such as lipopolysaccharides and cytolethal distending toxin-B
- Viral antigens, notably Epstein-Barr virus early antigen and EBNA.
- Human and bacterial heat shock proteins.
- Molds and mycotoxins, especially *Stachybotrys* and Satratoxin
- Some vaccines containing viral or bacterial antigens, toxic chemicals and food proteins.
- Chemicals such as DNP-BSA, food coloring and other neo-antigens.
- Medications with specific chemical structures that directly or indirectly form neo-antigens with human tissue.
- Bioactive nanoparticles containing chemicals, gelatin, dextran and human albumin.

- Lectins/Agglutinins, especially peanut and bean agglutinins.
- Seaweeds that contain a very high percentage of lectins which are glycoproteins or N-glycopeptides.
- Microbial transglutaminases (food/meat glue)
- Apoptotic cell components, nuclear antigens and ssDNA
- High fat diet
- High salt diet

Most research on immune polyreactivity has been done with serum immunoglobulins, however, there is a small body of polyreactivity research done in mucosal secretions,[6, 7] showing that polyreactivity can occur in both the mucosal and the systemic immune systems.

References:

1. Sigounas G, Harindranath N, Donadel G, Notkins AL. Half-life of polyreactive antibodies. J Clin Immunol, 1994; 14(2):134-140.
2. Dimitrov JD, Planchais C, Roumenina LT, et al. Antibody polyreactivity in health and disease: statu variabilis. J Immunol, 2013; 191:993-999.
3. Gunti S and Notkins AL. Polyreactive antibodies: function and quantification. J Infect Dis, 2015; 212(Suppl 1):S42-S46.
4. Mouquet H, Scheid JF, Zoller MJ, et al. Polyreactivity increases the apparent affinity of anti-HIV antibodies by heteroligation. Nature, 2010; 467(7315):591-595.
5. Eisen HN. Affinity enhancement of antibodies: how low-affinity antibodies produced early in immune responses are followed by high-affinity antibodies later and in memory B-cell responses. Cancer Immunol Res, 2014; 2(5):381-392.
6. Quan CP, Berneman A, Pires R, et al. Natural polyreactive secretory immunoglobulin A autoantibodies as a possible barrier to infection in humans. Infect Immun, 1997; 65(10):3997-4004.
7. Fukuyama Y, King JD, Kataoka K, et al. Secretory IgA antibodies play an important role in the immunity to *Streptococcus pneumoniae*. J Immunol, 2010; 185:1755-1762.