Perspective

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The Role of Polyreactive Antibodies in Prevention against Pneumococcal Infection

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Perspective

Antibodies are an important component of the immune response. They have the ability to attach their molecular targets with extreme sensitivity and specificity, offering protection against a wide range of infections. They have long been recognized as indicators of a successful immune response to vaccination and are now extensively produced as highly selective and powerful immunotherapeutic agents. Polyreactive antibodies, which may bind more than one target molecule and are present in serum, are less well known. We highlight recent study on naturally occurring polyreactive antibodies that indicates their relevance in protecting against Streptococcus pneumonia, a major cause of respiratory infection.

Human plasma contains antibodies against the xeno-carbohydrate terminal galactose-a-1-3-galactose (anti-αGal). These antibodies are common, accounting for around 1% of all immunoglobulins, and are found as IgG, IgM, and IgA. They might be produced in reaction to carbohydrates released by gut bacteria. The quantities of these anti-Gal antibodies, which can be of any isotype, vary greatly across individuals but can account for up to 1% of total IgG and more than 1% of total IgM. The role of anti-αGal antibodies in bacterial pathogen defense is unknown. While IgG antibodies are known to play an essential role in protective responses in the airways, the role of anti-αGal antibodies in this protection has not previously been investigated.

We report evidence that demonstrates the significance of anti-αGal antibodies in the protective immune response against Streptococcus pneumonia, a major cause of pneumonia that kills millions of people globally each year. Antibodies that recognize the highly diverse structural components of the bacterial capsule are important for disease protection, and the authors previously reported evidence that anti-αGal antibodies could react with pneumococci lacking the terminal Galα3Gal moiety, for which the anti-αGal antibodies are specific. This suggested that polyclonal human anti-αGal antibodies might identify a wider range of bacterial antigens. Antibodies that are 'polyreactive' have previously been hypothesized to be crucial in antibacterial immune responses.

Initial analyses of healthy controls and patients with airway infections indicated reduced anti-αGal levels in persons with recurrent lower airway infections, even when age and blood group antigen, which are recognized confounders, were adjusted for. An analysis of data from lung transplant candidates who commonly have lower airway infections found that this group had elevated anti-αGal levels. As a result, lower anti-αGal levels do not appear to be a result of recurring lower airway infections, but may contribute to their occurrence.

To further understand the specificity of anti-αGal IgG, the researchers tested reactivity against 91 S. pneumonia serotypes, finding positive responses in at least 48 of them. Of them, 37 are known to be devoid of the terminal Galα3Gal for which anti-αGal has a main specificity. Follow-up tests revealed that anti-α Gal IgG is polyreactive to a variety of bacterial polysaccharides and is blocked by the addition of soluble Galα3Gal; anti-α Gal may therefore be classified as polyreactive. Anti-αGal antibodies contribute significantly to overall anti-pneumococcal reactivity in individual samples, although this contribution varies greatly between persons, and anti-αGal IgG is varied in the pneumococcal strains to which it binds. Furthermore, because each individual's anti-αGal pool comprises a diverse set of specificities, it should be referred to as the plural 'anti-αGals' or 'anti-αGal antibodies.'

Previously, several scientists established that anti-αGal antibodies may activate complement in the same way as IgG antibodies do. In this study, they demonstrated that anti-αGal antibodies significantly enhanced the phagocytic activity of primary human blood leucocytes *in vitro*, again *via* a complement-dependent mechanism. They examined data from 29,034 reported instances of this reportable illness in Denmark between 1966 and 2014 to see if they could also safeguard the public from sickness. They discovered that commonly pathogenic subtypes responded poorly to anti-αGal, whereas the most anti-αGal reactive pneumococcal

subtypes produced invasive illness less frequently. As a result, these polyclonal anti-αGal antibodies may protect humans from invasive pneumococcal infections.

This is a significant study because it reveals the protective activities of polyreactive antibodies in the human population. Polyreactivity is frequently regarded as an inappropriate characteristic during the creation of therapeutic antibodies owing to the likelihood that off-target specificities may decrease the therapeutic impact or create unwanted consequences. As this study shows, a greater knowledge of how polyreactive antibodies give protection against antigenically diverse pathogens may lead to more effective ways for avoiding infection or reducing harmful autoimmune disease.