IgG4

IgG4 is a very dynamic antibody: the antibody is involved in a continuous process of half-molecules (i.e. a heavy and attached light-chain) exchange. This process, also referred to as 'Fab-arm exchange', results usually in asymmetric antibodies with two different antigen-combining sites. While these antibodies are hetero- bivalent, they will behave as monovalent antibodies in most situations. Another aspect of IgG4, still poorly understood, is its tendency to mimic IgG rheumatoid factor (RF) activity by interacting with IgG on a solid support. In contrast to conventional RF, which binds via its variable domains, the activity of IgG4 is located in its constant domains. This is potentially a source of false positives in IgG4 antibody assay results. Because regulation of IgG4 production is dependent on help by T-helper type 2 (Th2) cells, the IgG4 response is largely restricted to non-microbial antigens. This Th2-dependency associates the IgG4 and IgE responses. Another typical feature in the immune regulation of IgG4 is its tendency to appear only after prolonged immunization. In the context of IgE-mediated allergy, the appearance of IgG4 antibodies is usually associated with a decrease in symptoms. This is likely to be due, at least in part, to an allergen-blocking effect at the mast cell level and/or at the level of the antigen-presenting cell (preventing IgE-facilitated activation of T cells). In addition, the favourable association reflects the enhanced production of IL-10 and other anti-inflammatory cytokines, which drive the production of IgG4. While in general, IgG4 is being associated with non-activating characteristics, in some situations IgG4 antibodies have an association with pathology. Two striking examples are pemphigoid diseases and sclerosing diseases such as autoimmune pancreatitis. The mechanistic basis for the association of IgG4 with these diseases is still enigmatic. However, the association with sclerosing diseases may reflect an excessive production of anti-inflammatory cytokines triggering an overwhelming expansion of IgG4-producing plasma cells. The bottom line for allergy diagnosis: IgG4 by itself is unlikely to be a cause of allergic symptoms. In general, the presence of allergen-specific IgG4 indicates that anti-inflammatory, tolerance-inducing mechanisms have been activated. The existence of the IgG4 subclass, its up-regulation by anti-inflammatory factors and its own anti-inflammatory characteristics may help the immune system to dampen inappropriate inflammatory reactions [1].

IgG4-related disease and IgG4-mediated neurological autoimmune disorders: One and the same? [2].

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