SCIENCE @LERT

Function of immunoglobulin A in immunity

van Egmond M, van Garderen E, van Spriel AB, *et al.* FcαRI-positive liver Kupffer cells: reappraisal of the function of immunoglobulin A in immunity. *Nat Med* 2000;**6**:680–5.

Abstract
Despite the well-recognized involvement of immunoglobulin (Ig) A in mucosal immunity, the function of its receptor, FcαRI (CD89), is poorly understood. The ability of FcαRI to activate leukocytes seems to conflict with the proposed anti-inflammatory activity of secretory IgA. We show here that in a transgenic mouse model, inflammatory mediators induced expression of FcαRI on Kupffer cells, which enabled efficient phagocytosis in vivo of bacteria coated with serum IgA. Secretory IgA did not initiate phagocytosis. Therefore, interactions between serum IgA and FcαRI on Kupffer cells may provide a 'second line of defense' in mucosal immunity, by eliminating invasive bacteria entering through the portal circulation and thus preventing disease.

Comment

Immunoglobulin A (IgA) is by far the most abundant immunoglobulin in humans.[1] It is also the most heterogeneous. Serum IgA is mainly monomeric. It is produced by B lymphocytes in the bone marrow and in some lymphoid organs. Humans produce as much serum IgA as they do IgG. Most of the IgA in mammals is, however, found in mucosal secretions. Secretory IgA is dimeric or polymeric IgA associated with J chain and with secretory component, a part of the receptor involved in the secretion process.

Recent research[2] has suggested that secretory IgA in the gut comes from two sources. Approximately 75% is from B2 lymphocytes in organised germinal centres of mucosal lymphoid tissues such as Peyer's patches. This IgA production is T lymphocyte dependent. A second source, possibly contributing around 25% of the secretory IgA, is produced by B1 lymphocytes that develop in the peritoneal cavity and are distributed diffusely in the intestinal lamina propria. This IgA may represent a primitive T lymphocyte independent source of IgA recognising commensal bacteria. Given the abundance and complexity of IgA, it is difficult to envisage that it does not perform important functions in health and disease.

Identification and characterisation of a leucocyte Fc receptor for IgA (FcαR, CD89) present on neutrophils, eosinophils, and monocytes demonstrated an active role for IgA in immunity. Many studies have now shown that FcαR, on binding to aggregated IgA, triggers cellular functions such as degranulation and respiratory burst as efficiently, or more efficiently, than IgG. This is not surprising as the receptor is structurally related to the receptors for IgG (FcγRI, FcγRII, and FcγRIII) and to the high affinity receptor for IgE, FcεRI. Indeed, intracellular signalling via FcαR is transduced via the same intracellular peptide, the γ chain, which is used by IgG and IgE receptors. The properties of FcαR have been reviewed.[3 4]

Powerful incites into the functions of IgA, dependent on its interaction with FcαR, are being obtained by the use of transgenic mice expressing human FcαR.[5] In a series of papers, van Egmond *et al* have shown convincingly that FcαR can direct the killing of microorganisms and tumour cells coated with IgA.[6] Interestingly, in spite of much effort, no murine equivalent of this FcαR has yet been identified. Indeed, it might not exist. Rodent serum contains very little IgA. This IgA is dimeric (but lacks a secretory component). There is no murine equivalent of the 1–5 mg/ml monomeric IgA found in human serum. Mouse IgA does not bind to human FcαR.

In this publication, the Dutch group show that in the transgenic mouse model, human FcαR is expressed not only on circulating leucocytes but also on liver Kupffer cells. The liver has been known for many years to play a key role in IgA metabolism although it is not yet clear what its function might be. Unfortunately, many early studies came to the wrong conclusions because of differences in the binding of human and rat IgA to the asialoglycoprotein receptor and differences in the hepatic expression of the polymeric Ig receptor in humans and rodents. It has been recognised for many years that patients with severe liver damage have a marked increase in serum IgA concentration, including polymeric and secretory IgA.[7] Indeed, the experiments which led to the first identification of FcαR were the result of studies of an opsonic activity (IgA anti-yeast mannan antibodies) found in the serum of three Scottish men with alcoholic liver disease!

van Egmond *et al* demonstrate, immmunohistochemically, the expression of FcαR on Kupffer cells in the liver of the mouse transgene and in human liver. Expression in the transgene was increased by the action of granulocyte colony stimulating factor. In transgenic mice, Kupffer cells expressing FcαR were shown to mediate phagocytosis in vivo of *Escherichia coli* coated with serum IgA or secretory human IgA before injection. Secretory IgA was less efficient as an opsonin. In vitro, neutrophils from humans or transgenic mice phagocytosed bacteria opsonised with human serum IgA but not with human secretory IgA.

The different abilities of serum and secretory IgA to trigger phagocytosis is remarkable. We and others, including the Dutch group, have shown that secretory IgA binds to FcαR and can trigger leucocyte respiratory burst. It has been shown that purified secretory IgA binds to purified FcαR with the same affinity as serum IgA. Only one of the IgA molecules in the dimeric secretory IgA appears to be available[8]; the other is presumably shielded by the secretory component. Recent studies, so far limited to serum IgA, suggest considerable rigidity in the IgA molecule which may limit the density of deposition of IgA on an organism thereby controlling its opsonic potential.[9] It is clear that further investigation is necessary before the conflicting studies on the effector functions of secretory IgA can be resolved.

But what of the functions of FcαR on Kupffer cells? van Egmond *et al* suggest that in pathological conditions of the gut, characterised by a defective mucosal barrier and production of inflammatory mediators, expression of FcαR is induced in Kupffer cells. These phagocytes may remove

IgA opsonised bacteria from portal blood before full septicaemia can ensue. This is clearly one important scenario. The significance of increases in serum IgA associated with liver damage in inflammatory bowel disease is another, as is the association of liver disease with IgA nephropathy. Launay *et al* have recently shown that in their FcαR transgenic mice, IgA nephropathy develops spontaneously.[10] This is clearly a time of renewed interest in the role of IgA in the gut.

Characterisation of FcαR has challenged the paradigm of IgA as a non-inflammatory or even anti-inflammatory immunoglobulin. The existence of transgenic mice and knockouts for Fc receptors and very recent crystallographic evidence defining, in detail, the interaction of IgG with FcγRIII and IgE with FcεRI suggests that there will be renewed interest, in general, in the role in immunoglobulins in immunity and inflammation.

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