Immunoglobulin A (IgA) is by far the most abundant component of mucosal immune system, 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.

Powerful incites into the functions of IgA, dependent on its interaction with FcαRI, are being obtained by the use of transgenic mice expressing human FcαRI. In a series of papers, van Egmond et al have shown convincingly that FcαRI can direct the killing of microorganisms and tumour cells coated with IgA. Interestingly, in spite of much effort, no murine equivalent of this FcαRI 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 FcαRI.

In this publication, the Dutch group show that in the transgenic mouse model, human FcαRI 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. Indeed, the experiments which led to the first identification of FcαRI 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, immunohistochemically, the expression of FcαRI 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 FcαRI 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 FcαRI and can trigger leucocyte respiratory burst. It has been shown that purified secretory IgA binds to purified FcαRI with the same affinity as serum IgA. Only one of the IgA molecules in the dimeric secretory IgA appears to be available; 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. 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 FcαRI 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 FcαRI is induced in Kupffer cells. These phagocytes may remove...
IgA opsonised bacteria from portal blood before full septicemia 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. 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 FcαRIII and IgE with FcαRI suggests that there will be renewed interest, in general, in the role in immunoglobulins in immunity and inflammation.

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