COMPLEMENT FRAGMENT C3d INHIBITS TLR9 AND BCR+TLR9 INDUCED ACTIVATION OF HUMAN B CELLS

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Introduction/Background

Complement receptors type 1 (CR1, CD35) and 2 (CR2, CD21) expressed by B lymphocytes play a crucial role in bridging innate and adaptive immunity. By binding different degradation products of the third complement component, C3 – such as C3b and C3d - these two receptors mediate opposing effects in human B lymphocytes. Namely, CR2 enhances the BCR mediated functions while CR1 inhibits those (Int. Immunol. 2013, J. Immunol. 2002).

Several microbial pathogens not only engage BCR but can trigger B cell functions by binding to Toll-like receptor 9 (TLR9), the microbial DNA sensor of the innate immune system. Besides the BCR dependent signalling, TLR9 also significantly determines the activation state of a B lymphocyte. Moreover, it is also known that, theTLR9 and BCR initiated signalling pathways synergise at the level of MAPKs.

Methods

Our aim is to get insight into how complement receptors – especially CR2 – might influence the TLR9 induced activation of human B cells. For the experiments we used C3d, the natural ligand of CR2 immobilized on the surface of the culture plates, and measured the proliferation and phosphorylation of human resting tonsillar B cells. Cells were stimulated via BCR using suboptimal dose of $F(ab')_2$ anti-human IgG/M/A and via TLR9 using CpG ODN 2006 either separately or simultaneously.

Results and Conclusions

We show that clustering of CR2 by its natural ligand significantly reduces both the TLR9 and BCR+TLR9 induced proliferation of resting human tonsillar B cells. These results demonstrate that CR2 exerts a strong inhibitory effect on TLR9 dependent signalling, which can not be prevailed by BCR triggering. To see whether additional B cell functions are also affected by the engagement of CR2, the assessment of antibody production and cytokine release is in progress in our laboratories.

Our results reveal a so far undescribed level of B cell regulation where complement might be strongly involved.