EXPRESSION AND FUNCTION OF C3 AND C3AR IN HUMAN B CELLS - A NOVEL CROSS-TALK BETWEEN COMPLEMENT, TLRS AND ADAPTIVE IMMUNITY

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Introduction: In addition to generating an immediate response against invading pathogens, the complement system is also involved in initiating and shaping the adaptive immune response via its activation products. One of the major cleavage fragments of the complement component C3, C3a, and its receptor (C3aR) have recently been shown to regulate T cell activation in both autocrine and paracrine manners. Since earlier studies regarding the expression and role of C3aR in human B cells are controversial, we decided to reinvestigate how C3/C3a might be involved in the regulation of certain B cell responses.

Methods: Expression of C3 and C3aR was investigated at the mRNA level by RT-PCR and at the protein level by flow cytometry, confocal microscopy and Western Blot. In functional experiments, resting tonsillar B cells were stimulated through the BCR and/or TLR9; and cytokine or Ig-secretion were assessed by ELISA. The phosphorylation level of intracellular molecules was investigated with Western Blot.

Results: We found that human B cells express C3 as well as C3aR both at the mRNA and at the protein level. While C3 appeared both intracellularly and at the cell surface, C3aR was expressed only inside the cell. C3a was chemotactically active on B cells even at nanomolar concentrations. Activation of the cells via the B cell receptor (BCR) or the Toll-like receptor 9 (TLR9) resulted in a twofold increase in the amount of intracellular C3 as well as C3aR, however the receptor could not be detected at the cell surface even after activation.

Incubation of B lymphocytes with C3a resulted in enhanced phosphorylation of AKT and mitogen-activated protein kinases, like p38, however IL-6 and IL-10 production and Ig-secretion was suppressed in a dose-dependent manner. Additionally, B-cell derived C3 and C3aR had a positiv impact on allogeneic stimulation of T cells.

Conclusion: These results suggest that C3 and C3aR have a direct immunomodulatory effect on BCR- and TLR9-induced effector functions of B cells and reveal a novel interaction point between complement, TLRs and adaptive immunity.