Involvement of B-cell Adaptor for Phosphoinositide 3-Kinase in modulating crosstalk between the Phosphoinositide 3-Kinase, Toll-like receptor, and Phospholipase C γ2 signalling pathways

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B cell Adaptor for Phosphoinositide 3-kinase (BCAP) is an adaptor for Phosphoinositide-3-kinase (PI3K) and also Toll-like receptors (TLRs) during inflammation where it acts as negative regulator. It has also been shown to associate with p85, the regulatory subunit of PI3K and with two TIR domain containing proteins from the TLR pathway MyD88 and TIRAP, and consequently, has been assumed to possess a TIR-domain.

A primary aim of this thesis was to determine whether BCAP possesses an N-terminal TIR-domain and to understand its role in promoting crosstalk between the PI3K, PLCγ2, and TLR pathways. The high resolution x-ray crystal structure of the N-terminal domain of BCAP comprising residues 7 to 142 has been solved and structural comparisons firmly establish that it belongs to the TIR family of proteins. Additionally, we have shown that BCAP interacts directly with TLR2, TLR4, TIRAP and p85 of PI3K, and forms a large signalling complex which includes PI3K and PLCγ2. BCAP is also shown to be phosphorylated by the non-receptor tyrosine kinases Lyn and Syk, an event that enhances its binding to p85, and the subsequent mapping of the phosphorylated forms of BCAP has enabled the identification of several phosphorylation sites in its sequence.

BCAP appears to modulate the TLR signalling pathway by associating with both PLCγ2 and PI3K, both of which utilise PIP2, an important constituent of the plasma membrane. PIP2 utilization deprives TIRAP of its anchor to the plasma membrane and prevents the endocytosis of TLR4 upon its stimulation, thus negatively regulating the TLR4.