Abstract

The pentameric, but not the monomeric, isoform of C-reactive protein (CRP) enhances phagocytosis of methicillin-resistant *Staphylococcus aureus* (MRSA); potential implications for treatment strategies.

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Evidence indicates C-reactive protein (CRP) is not only a marker of infection but has a protective role, principally through the activation of complement and opsonisation of bacterial pathogens. However, of the two isoforms of CRP, native-CRP (nCRP) and monomeric-CRP (mCRP), it is unknown which isoform confers protection against bacterial infections. The aim of this study was to determine the effect CRP isoforms on macrophage-mediated clearance of methicillin-resistant *Staphylococcus aureus* (MRSA) in an *in vitro* phagocytosis assay using concentrations of mCRP (100µg/ml and 250µg/ml) or nCRP (500µg/ml and 1000µg/ml) that reflect acute human inflammatory responses. CRP-induced phagocytosis was explored further using wortmannin, SB203580 and PD98059 to inhibit phosphatidylinositol 3-kinase (PI3K), p38 mitogen-activated protein kinase (MAPK) and MAPK/ extracellular signal-regulated kinase (MAPK/ERK) pathways respectively.

Treatment with mCRP had no significant ($P>0.05$) effect on MRSA clearance compared to the untreated control, whereas nCRP significantly ($P<0.01$) increased phagocytosis of MRSA in a concentration-dependent manner. The nCRP-induced phagocytosis was significantly ($P<0.01$) reversed by inhibiting PI3K, p38 MAPK or MAPK/ERK (MEK). These findings suggest dissociation of nCRP to mCRP at sites of infection may lead to impaired bacterial clearance whereas local blockade of mCRP formation may be a viable therapeutic strategy for MRSA infections.