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Evolution of host-defense function of C-reactive protein from horseshoe crab to humans

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Abstract

C-reactive protein (CRP) has been conserved throughout evolution. Human native CRP exhibits calcium-dependent binding specificity for phosphocholine. Human CRP in its non-native structure expresses the capability to bind to deposited and conformationally-altered proteins and which can be achieved by several means including treatment of CRP with acidic pH. The ligand-binding property of human CRP in its non-native structure has implications for toxic and inflammatory conditions and favors the conservation of CRP throughout evolution. It is not known, however, whether CRP from invertebrates exhibits structure-based ligand-binding properties similar to that of human CRP. The aim of this study was to investigate the ligand-binding properties of CRP from the American horseshoe crab *Limulus polyphemus*. We used oxidized low-density lipoprotein (ox-LDL) immobilized on microtiter plates as a model for deposited and conformationally-altered proteins. We found that Limulus CRP binds to ox-LDL at physiological pH, in contrast to human CRP which requires acidic pH to do so. The binding of Limulus CRP to ox-LDL occurred even in the absence of calcium, suggesting that the binding was not mediated through exposed phosphocholine molecules, if any, on ox-LDL. We conclude that the host-defense function of CRP evolved with the development of the immune system to expose a ligand-binding specificity only when needed, that is, an inflammatory microenvironment would have to be sensed by CRP and that CRP would change its structure to execute its function. Limulus CRP also provides us with a tool to investigate the structure-function relationships of human CRP in animal models of inflammation.