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Review

C-reactive protein and lung diseases

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ABSTRACT

C-reactive protein (CRP), a member of the pentraxin family of plasma proteins, is one of the most distinctive acute phase reactants. In response to inflammation, cell damage or tissue injury, plasma level of CRP rapidly and dramatically increases up to 1000-fold, a phenomenon that has been used for years to monitor infections and many destructive/inflammatory conditions. The magnitude of CRP increase usually correlates with the severity of injury or inflammation and reflects an important physiological role of this interesting but still under-investigated protein. It is now generally accepted that CRP is involved in host defense and inflammation. However, the exact function of this protein in health and disease remains unclear. Many studies have demonstrated that in different pathophysiological conditions CRP might be involved in the regulation of lung function and may participate in the pathogenesis of various pulmonary disorders. The fluctuation of CRP concentrations in both alveolar fluid and serum associated with different pulmonary diseases suggests its important role in lung biology. Discussion of the still controversial functions of CRP in lung physiology and diseases is the main focus of this review.

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Abbreviations: CRP, C-reactive protein; PC, phosphocholine; ChoP, phosphorylcholine; snRNP, small nuclear ribonucleic protein; IL-6, -8, 1β, interleukin 6,8, 1β; TNFα, tumor necrosis factor α; ufCP, ultrafine carbon particles; PM, pollution particles; Hsp70, heat-shock protein 70; LPS, lipopolysaccharide; FEV, forced expiratory volume; FVC, force vital capacity; BMI, body mass index; ESP, eosinophil cationic protein; BAL, bronchoalveolar lavage; fMLP, formyl-Met-Leu-Phe; HFn, human plasma fibronectin; ARDS, acute respiratory distress syndrome; BO, bronchiolitis obliterans; BHR, bronchial hyperresponsiveness; COPD, chronic obstructive pulmonary syndrome; SIRC, systemic inflammatory response syndrome; SNP, single nucleotide polymorphism; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; PEF, peak expiratory flow; ECP, eosinophil cationic protein; ICU, intensive care unit; VAP, ventilator-associated pneumonia; STAT, signal transducer and activator of transcription; C/EBP, CCAAT/enhancer-binding protein; NF-κB, nuclear factor kappa-light-enhancer of activated B cells; MAPK, mitogen-activated protein kinase.

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1. Introduction

C-reactive protein (CRP), a prototypical acute-phase protein in humans and other animal species, is one of the most frequently used markers of inflammation. CRP is known to be synthesized by liver cells in response to pro-inflammatory cytokines (Marnell et al., 2005). CRP concentrations in blood are typically extremely low in healthy individuals, but may be fast increased after induction of inflammatory response associated with infections, autoimmune and cardiovascular diseases, as well as sepsis and cancer. Raised CRP level can also be a predictor of cardiovascular diseases and is used as a marker of systemic inflammation in various conditions. For instance, after sepsis, acute myocardial infarction or tissue damage, serum levels of CRP elevated in some cases up to 1000-fold within 1–2 days in correlation with the magnitude of tissue injury or the severity of inflammation.

CRP binds to normal cells, including platelets, phagocytes, and others, as well as to dead or damaged cells. When CRP is bound to pathogens or dying/dead cells, it is recognized by a complement component C1q and activates the classical complement pathway or may also stimulate responses from phagocytic cells via the binding to Fcγ receptors (Marnell et al., 2005; Mold et al., 2002a). Thus, CRP can identify a number of pathogens and altered cells and, therefore, induce their removal by the humoral arm of innate immunity. However, the great number of records indicate that CRP has both the destructive, as well as protective effects (Griselli et al., 1999; Torzewski et al., 2000; Zwaka et al., 2001). CRP that may serve as a predictor of cardiovascular risk is involved in the pathogenesis of arteriosclerotic lesions and can increase tissue damage in acute myocardial infarction and other inflammatory diseases (Berton et al., 2003).

Recent observations suggest that a high level of CRP could be involved in the pathogenesis of cancer. For instance, CRP is a systemic biomarker of reduced lung function and a predictive marker in cystic fibrosis and chronic obstructive pulmonary disease that can also serve as a systemic biomarker of lung inflammation. CRP which is produced locally in the lungs in addition to being released by the liver cells is very important as well. However, its exact function in the lungs and the pathways mediating its involvement in different lung pathologies are not revealed.

New mechanistic, systematic and clinical studies are needed to understand the role of CRP in lung function and lung diseases. These findings could have broad implications. If an unusual role of CRP in the pulmonary tissue is confirmed, some of the conventional knowledge regarding the role of CRP in human diseases may require reappraisal.

2. CRP biology

2.1. CRP structure

CRP (PDBs: 1BO9; 1CRV; 1GNH; 1LJ7; 3L2Y; 3PVN) is a protein with an annular pentameric disk shape belonging to the pentraxin protein family. It consists of the cyclical arrangement of five identical non-covalently bound subunits (protomers) set symmetrically around a central pore (Fig. 1) (Gupta et al., 2012; Shrive et al., 1996; Thompson et al., 1999). Each subunit is oriented into two antiparallel β-sheets and binds two Ca^{++} ions, which participate in the binding of some of its ligands to stabilize the subunit structure. The recognition face of the protomer has a phosphocholine binding site consisting of two calcium ions adjacent to a hydrophobic pocket (Fig. 1). Two key residues, Phe^{66} and Glu^{81} promote the binding of CRP to phosphocholine (PC) (Agrawal et al., 2002; Black, 2003; Black et al., 2003; Thompson et al., 1999). The opposite face of pentamer binds complement Cq1and Fcγ receptor, whose binding sites are overlapping (Gupta et al., 2012). The CRP interactions are accompanied by conformational changes in CRP structure depending on the ligand to which CRP is bound (Black et al., 2004; Gaboriaud et al., 2003).

2.2. CRP ligands

Phosphocholine is the most characterized CRP ligand that initiates recognition and phagocytosis of damaged cells (Pepys and Hirschfield, 2003) and is responsible for the binding to microorganisms (Bodman-Smith et al., 2002; Volanakis and Kaplan, 1971).

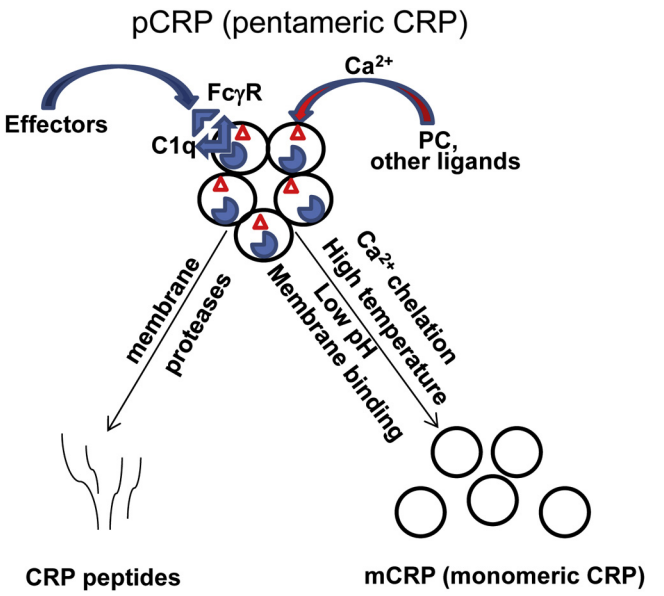

Fig. 1. Structural features of C-reactive protein. Soluble native CRP normally circulates in the blood as a symmetrical disk-shaped pentamer with subunits arranged in an annular pattern on the same planer face. Each of the five CRP monomers has a single site for PC or other ligand binding (), and a single diametrically opposed site that binds effector molecules C1q and/or FcγR (). In the presence of Ca^{2+}, one of the pentamer units provides attachment to any surface displaying the appropriate ligands, while the other face of the ligand-bound protein displays multiple sites for binding C1q and/or FcγR. Thus, the conformation of the native molecule is determined by Ca^{2+} and can be converted to altered forms by removal of Ca^{2+}, high temperature, or acidic environment, or to proteolytic forms by digestion with serine proteases.