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PRO AND ANTI-INFLAMMATORY RESPONSES. CD14 AND THE LINK BETWEEN INNATE AND ADAPTATIVE IMMUNITY

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It has been extensively documented that CD14 acts as a critical mediator of bacterial recognition by the innate immune system. However, more recent evidence suggests that CD14 may perform other functions during the course of immune response. Indeed, it has been demonstrated that the soluble form of CD14 (sCD14) interacts directly (without participation of bacteria) with human T cells and acts as negative regulator of T cell activation and function.

Furthermore, interaction of sCD14 with human B cells results in a differential regulatory effect on immunoglobulin production. Notably, high concentrations of a soluble form of CD14 have been found in human breast milk. This milk-derived sCD14 was demonstrated to play a pivotal role in bacterial recognition by intestinal epithelial cells (IEC) and responses including IEC production of potent proinflammatory molecules.

Together, the recent findings support the contention that sCD14 performs a dual role in the immune response: as a sentinel, sensing the presence of bacteria, and as a physiological regulator of cellular and humoral immune responses, thus serving as a link between innate and adaptive immunity.

REGULATORS OF COMPLEMENT: BIOLOGICAL ROLES AND APPLICATIONS TO THERAPY

THE UNIQUE COMPLEMENT REGULATOR CD59: FUNCTIONAL CHARACTERISATION AND GENE DELETION

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The complement system, an essential factor in host defence against infection, is a double-edged sword with considerable potential to damage self tissues. To limit damage to self, a battery of protective proteins have evolved that regulate complement both in plasma and on cell membranes. At least three membrane proteins (CD35, CD46, CD55) regulate in the activation pathways but only a single membrane regulator of the cytolytic membrane attack pathway, termed CD59, has been characterised.

CD59 was first identified in 1988 as an activity in extracts of human erythrocytes that inhibited complement lysis of cells. We first showed that CD59 locked tightly into the forming membrane attack complex (MAC) and prevented formation of the lytic pore, then undertook to identify active sites in CD59 that permitted tight binding to the forming membrane attack complex. Several approaches have identified a single region, a groove on the membrane-distal face of CD59, that is essential for function and permits binding to the MAC. This information is being used to design anti-complement therapeutics.

Recently we have undertaken to delete the gene encoding CD59 in the mouse. Mice deficient in CD59 were born in the predicted numbers and were apparently healthy. The CD59-negative mouse display spontaneous intravascular haemolysis and haemoglobinuria, a phenotype that closely resembles the human haemolytic disorder paroxysmal nocturnal haematuria (PNH). In PNH, a failure in glycosyl phosphatidylinositol (GPI) anchor biosynthesis in a haemopoietic stem cell clone yields erythrocytes deficient in the complement regulators CD55 and CD59 (because both are GPI anchored) and are consequently highly susceptible to lysis by complement. In the CD59-deficient mice, systemic activation of complement causes further haemolysis. The effects of CD59 deficiency on other circulating cells and on endothelia in the mouse are currently being evaluated.