

HELSINGIN YLIOPISTO – HELSINGFORS UNIVERSITET – UNIVERSITY OF HELSINKI

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Tekijä – Författare – Author Juha Hakulinen			
Työn nimi – Arbetets titel – Title Isolation and characterization of functionally active glycolipid-anchored complement lysis inhibitor protectin (CD59) from human milk			
Opplaine – Läroämne – Subject General microbiology			
Työn taso – Arbetets art – Level Pro gradu		Aika – Datum – Month and year April 1997	Sivumäärä – Sidoantal – Number of Pages 50 pages + supplement
Tiivistelmä – Referat – Abstract <p>The complement (C) system is made up of some 30 distinct proteins that are present in blood plasma and on cell membranes as precursor enzymes, effector molecules and control proteins. The principal function of the C system is to defend the host against microbial infections. The activation of C triggers a series of reactions that generate the so called membrane attack complex (MAC) on the activating surface. MAC is a pore-like lesion that destabilizes the target cell membrane resulting in cell lysis. Two pathways have been distinguished by which the complement system can become activated. Activation of the classical pathway is triggered by immunoglobulins (IgG and IgM), while the activation of the alternative pathway is nonspecific and is triggered directly by the target surface.</p> <p>Activated complement may be cytotoxic also to the host cells. However, normal cells can resist the cytolytic activity of complement by expressing several regulatory proteins on their cell surface. On the cell membranes several inhibitor molecules have been described (C8bp, CD35, CD46, CD55 and CD59). Two of these (C8bp and CD59 or protectin) have been demonstrated to directly inhibit the formation of MAC. CD59 is a 18 - 24 kDa glycoprotein that is anchored to cell membranes via a glycoposphoinositol (GPI) moiety. Protectin is widely distributed on human blood cells and on endothelial and epithelial cells of several organs. In addition to various cell membranes phospholipid-tailed protectin has been found in amniotic fluid and in seminal plasma, where it has been shown to be associated with extracellular organelles called prostasomes. Soluble, lipid-free forms of protectin have been isolated from human urine and produced in recombinant form but they have only a relatively weak complement lysis inhibiting activity.</p> <p>Because of its activities as an inflammation-inducing and cytolytic system, complement can increase tissue damage in many disorders. It has been suggested that the activation of the complement system may be involved in the development of tissue injury during myocardial infarction. Another example of pathologic C activation is paroxysmal nocturnal haemoglobinuria (PNH) where host blood cells become lysed by the autologous C system. PNH is a human disease characterized by a deficiency of GPI-anchored glycoproteins. Because of its activities CD59 is a candidate molecule for the treatment of PNH or in conditions where MAC causes tissue damage.</p> <p>In the present study the physiology and function of protectin have been analyzed in human breast milk. Milk is rich in fat droplets, milk fat globules (MFG), that are enveloped in a plasma membrane derived from the secretory cells of the mammary gland. The membranes of the MFG contain a variety of glycoproteins expressed by mammary epithelial cells. Both immunofluorescence and immunoblotting analysis demonstrated that protectin is strongly expressed on human MFG. In SDS-PAGE analysis MFG-protectin (CD59M) appeared as distinct bands with apparent Mr:s from 19 to 23 kDa similarly as protectin extracted from MCF7 breast carcinoma cells and erythrocyte membranes. CD59M in breast milk was functionally active and had a glycopospholipid-anchor as judged by its ability to incorporate into quinea pig erythrocytes and inhibit their lysis by human complement. These results indicate that functionally active protectin becomes enriched in milk fat globules and imply that secretion of GPI-anchored molecules e.g. into cow milk could be exploited as a means to produce bioactive molecules that need to be targeted into cell membranes.</p>			
Avalnsanat – Nyckelord – Keywords CD59, protectin, complement, milk fat globule, glycoposphoinositol			
Säilytyspaikka – Förvaringställe – Where deposited The library of General Microbiology Division at the Dept. of Biosciences			
<p>Muuta tietoja – Övriga uppgifter – Further information This study was carried out at Haartman-institute, Department of Bacteriology and Immunology, University of Helsinki. Part of the study has been published in Immunology: Hakulinen, J. and Meri, S. (1995) Shedding and enrichment of the glycolipid anchored complement lysis inhibitor protectin (CD59) into milk fat globules. Immunology 85, 495-501.</p>			