Molecular Immunology 56 (2013) 563–573

Contents lists available at SciVerse ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Review

Review of phosphocholine substituents on bacterial pathogen glycans: Synthesis, structures and interactions with host proteins☆

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ARTICLE INFO

Article history:
Received 26 March 2013
Received in revised form 24 May 2013
Accepted 28 May 2013

Keywords:
C-reactive protein
Haemophilus influenzae
Phosphocholine
Streptococcus pneumoniae

ABSTRACT

Among the non-carbohydrate components of glycans, the addition of phosphocholine (ChoP) to the glycans of pathogens occurs more rarely than acetylation or methylation, but it has far more potent biological consequences. These arise from ChoP's multiple interactions with host proteins, which are important at all stages of the infection process. These stages include initial adherence to cells, encountering the host's innate immune system and then the adaptive immune system. Thus, in the initial stages of an infection, ChoP groups are an asset to the pathogen, but they can turn into a disadvantage subsequently. In this review, we have focussed on structural aspects of these phenomena. We describe the biosynthesis of the ChoP modification, the structures of the pathogen glycans known to carry ChoP groups and the host proteins that recognize ChoP.

1. Introduction

The history of the investigation of ChoP–Ag interactions with host proteins dates back to the 1940s when Avery and colleagues (Abernathy and Avery, 1941; MacLeod and Avery, 1941a,b) described the reaction of C-substance from *Streptococcus pneumoniae* (PnC) with an acute phase protein from serum, which they termed C-reactive protein (CRP). These reports provided a molecular basis for the earlier serological observations of Tillett and Francis (1930). Thirty years later, it was found that this interaction was mediated by ChoP groups on the PnC (Volanakis and Kaplan, 1971; Leon and Young, 1971). A pathway and corresponding gene locus for ChoP modification was first described in *Haemophilus influenzae* by Weiser et al. (1997), and homologs of the four genes in the *lic1* locus were found in *S. pneumoniae* (Zhang et al., 1999). These two bacteria, one being gram-negative and the other gram-positive, have continued to be the major ones for the investigation of the properties of ChoP-modified glycans.

Despite the relative rarity of the ChoP modification, it is extraordinarily diverse, occurring on all of the major classes of bacterial polysaccharides and attached to different hydroxyls on a variety of hexoses. As will be summarized here, ChoP-modified glycans can interact with several different host proteins, which can aid cellular uptake but also renders the bacteria susceptible to attack from proteins of both the innate and adaptive immune systems. It therefore has a far more significant effect on polysaccharide properties than the more common modifications of acetylation or methylation, which only modulate antigenic structure. For a more complete description of the microbiology of the ChoP modification, see the recent review by Clark and Weiser (2013). While ChoP is the focus of this review, it should be noted that glycans modified with the related compound phosphoethanolamine will share some of the properties of ChoP-modified glycans.

2. Biosynthesis of the ChoP modification

ChoP groups are synthesized and added to glycans by the actions of proteins from *lic* gene clusters. In *H. influenzae*, the genes are subject to phase variation, leading to gain or loss of the ChoP modification, which then modulates the interactions of the bacteria with host proteins. The overall biosynthetic process is summarized in Fig. 1.

2.1. Obtaining choline

Bacteria do not synthesize choline themselves but acquire it from the host, aided by phosphodiesterases such as the *H.*

Abbreviations: ChoP, choline phosphate; PnC, pneumococcal C substance; CRP, C reactive protein; PAF, platelet-activating factor; LTA, lipotechoic acid; TAA, 2-acetamido-4-amino-2,4,6-trideoxyhexose; ZPS, zwitterionic polysaccharide.

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http://dx.doi.org/10.1016/j.molimm.2013.05.237

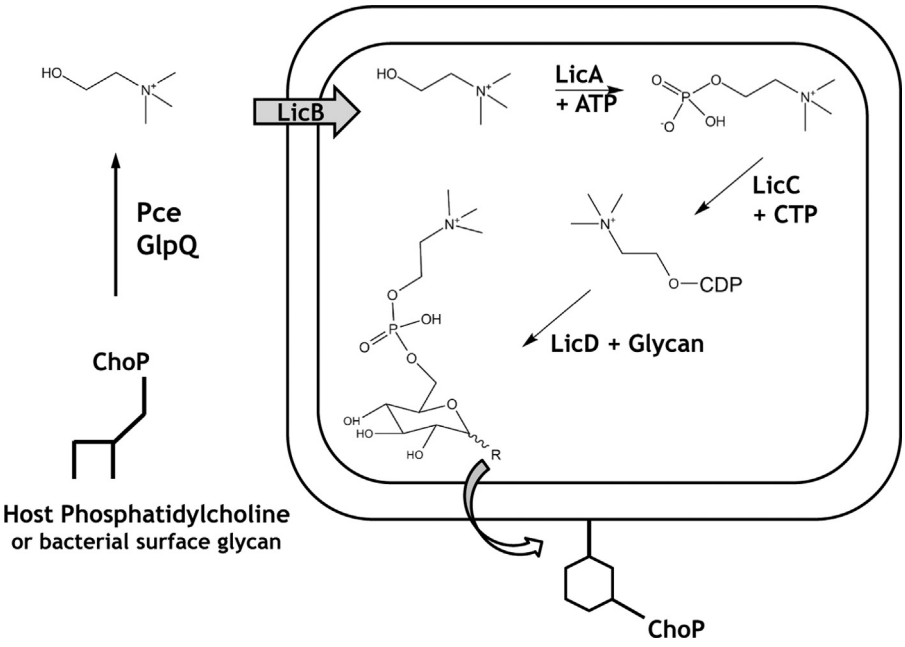

Fig. 1. Bacterial acquisition of ChoP groups on glycans. Bacteria aquire ChoP through its removal from host phosphotidylcholine, or bacterial surface ChoP containing glycans with the phosphodiesterases GlpQ and Pce. Cho is imported into cells and then converted to the activated form CDP-Cho via the action of LicA (kinase) and LicC (CDP-Cho synthetase). CDP-Cho is then a donor for the addition to glycans via ChoP transferase, LicD.

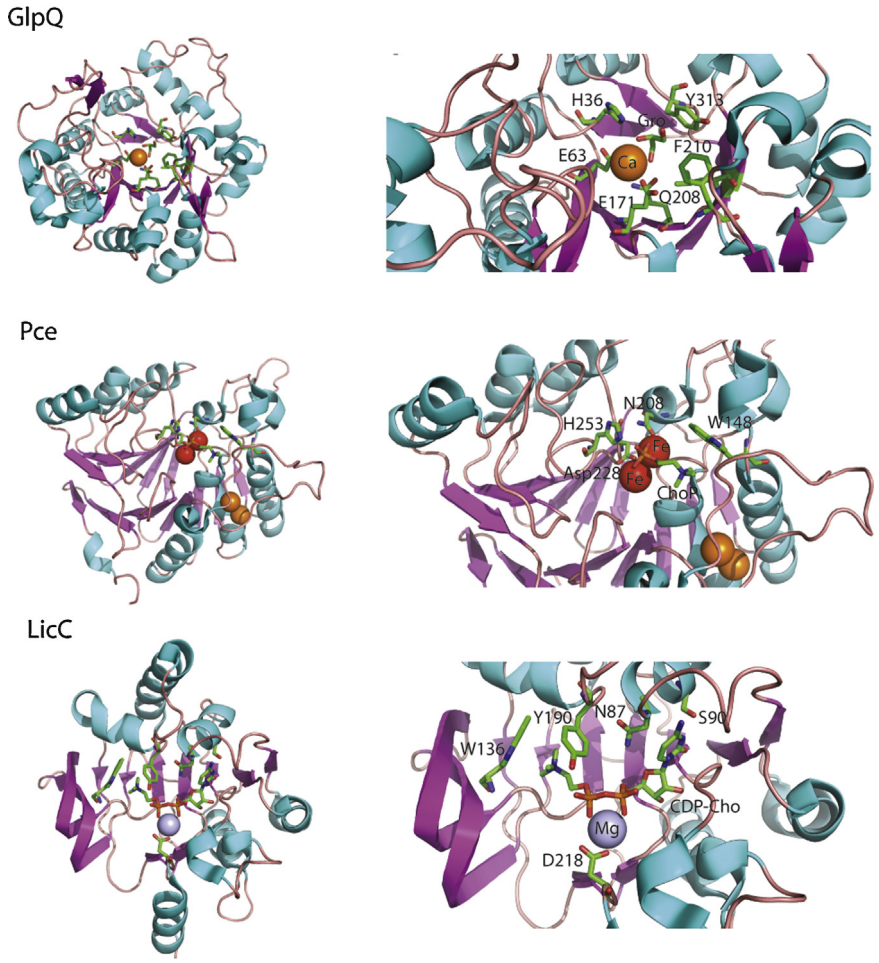

Fig. 2. Crystal structures of ChoP biosynthetic enzymes. The active sites of the protein have been shown with relevant amino acid side chains as stick representations and the metal ions as spheres. The views were created with The PyMOL Molecular Graphics System, Version 1.5.0.4 Schrödinger, LLC. Choline phosphodiesterases, GlpQ (PDB codes 1YDY and 1T8Q) and Pce (PDB 1WRA and 2BIB, LicC (PDB 1JYK and 1JYL). GlpQ contains glycerol, Pce contains choline phosphate, and LicC contains CDP-Cho.