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Research review paper

Glycosyltransferase-catalyzed synthesis of bioactive oligosaccharides

Carel A.G.M. Weijers, Maurice C.R. Franssen *, Gerben M. Visser

Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands

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ABSTRACT

Mammalian cell surfaces are all covered with bioactive oligosaccharides which play an important role in molecular recognition events such as immune recognition, cell–cell communication and initiation of microbial pathogenesis. Consequently, bioactive oligosaccharides have been recognized as a medicinally relevant class of biomolecules for which the interest is growing. For the preparation of complex and highly pure oligosaccharides, methods based on the application of glycosyltransferases are currently recognized as being the most effective. The present paper reviews the potential of glycosyltransferases as synthetic tools in oligosaccharide synthesis. Reaction mechanisms and selected characteristics of these enzymes are described in relation to the stereochemistry of the transfer reaction and the requirements of sugar nucleotide donors. For the application of glycosyltransferases, accepted substrate profiles are summarized and the whole-cell approach versus isolated enzyme methodology is compared. Sialyltransferase-catalyzed syntheses of gangliosides and other sialylated oligosaccharides are described in more detail in view of the prominent role of these compounds in biological recognition.

Contents

* Corresponding author. Tel.: +31 317 482976; fax: +31 317 484914.
E-mail address: maurice.franssen@wur.nl (M.C.R. Franssen).

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1. Introduction

Oligosaccharides (or glycans) are a major class of naturally occurring carbohydrates consisting of 3 to 10 monosaccharides. Oligosaccharides play a fundamental role in many important biological processes and are commonly found in Nature as glycoconjugates (glycoproteins or glycolipids). They show a high structural diversity, greatly exceeding the diversity of proteins (oligopeptides) and nucleic acids (oligonucleotides) (Raman et al., 2005).

The structural diversity of oligosaccharides produced by eukaryotes is determined by their biosynthesis in the endoplasmic reticulum (ER) and Golgi apparatus in the cell, in an assembly-line-like process that is not template driven (thus being unlike the template driven synthesis of proteins) and is subject to multiple sequential enzymatic pathways (Varki, 2006; Ohtsubo and Marth, 2006).

Although prokaryotes, archaea and bacteria, lack the cellular organelles that are found in eukaryotes, similar processes for oligosaccharide biosynthesis have been conserved. In these processes, the bacterial periplasm is equivalent to the eukaryotic ER during biosynthesis of N-linked oligosaccharides. O-linked oligosaccharides are formed in the bacterial cytoplasm or at the interface between cytoplasm and surface appendages such as pili and flagella (Szymanski and Wren, 2005). Pili and flagella are filamentous polymeric appendages composed of glycoproteins that protrude from the bacterial surface (Faridmoayer et al., 2007; Logan, 2006). Pili are involved in intercellular connection and transfer of plasmids between bacteria, whereas the flagellum is the key component of bacterial motility. A large number of bacteria also produce extracellular or capsular polysaccharides. From the latter, lipopolysaccharides (LPS) are the major extracellular components expressed by Gram-negative bacteria. A specific group of mucosal pathogenic bacteria produces cell-surface lipooligosaccharides (LOS) which have distinct features from the enterobacterial LPS compounds. Structures displayed in LOS have several structural similarities to human glycolipids and thus provide these pathogens with a means of evading the host immune response through molecular mimicry with high potent virulence (Brandenburg et al., 2003; Wakarchuk et al., 1998). Oligosaccharide antibiotics are another group of carbohydrate-containing bioactive compounds which are produced by several microorganisms, actinomycetes in particular. During biosynthesis, polar sugar components are enzymatically added to hydrophobic macrolide and tetracyclic structures, thereby increasing water solubility and creating recognition elements for interaction with potential targets. Addition of sugar moieties is commonly performed at very late stages of assembly and thus gives the producer-microorganism the possibility for the introduction of variation into antibiotic structures. The glycosylating enzymes involved are referred to as 'antibiotic glycosyltransferases' (Walsh et al., 2003; Luzhetskyy et al., 2005; Blanchard and Thorson, 2006; Thibodeaux and Liu, 2007a; Liang and Qiau, 2007).

In eukaryotes, bioactive oligosaccharides can commonly be found on the cell surface where they are involved in cell growth and

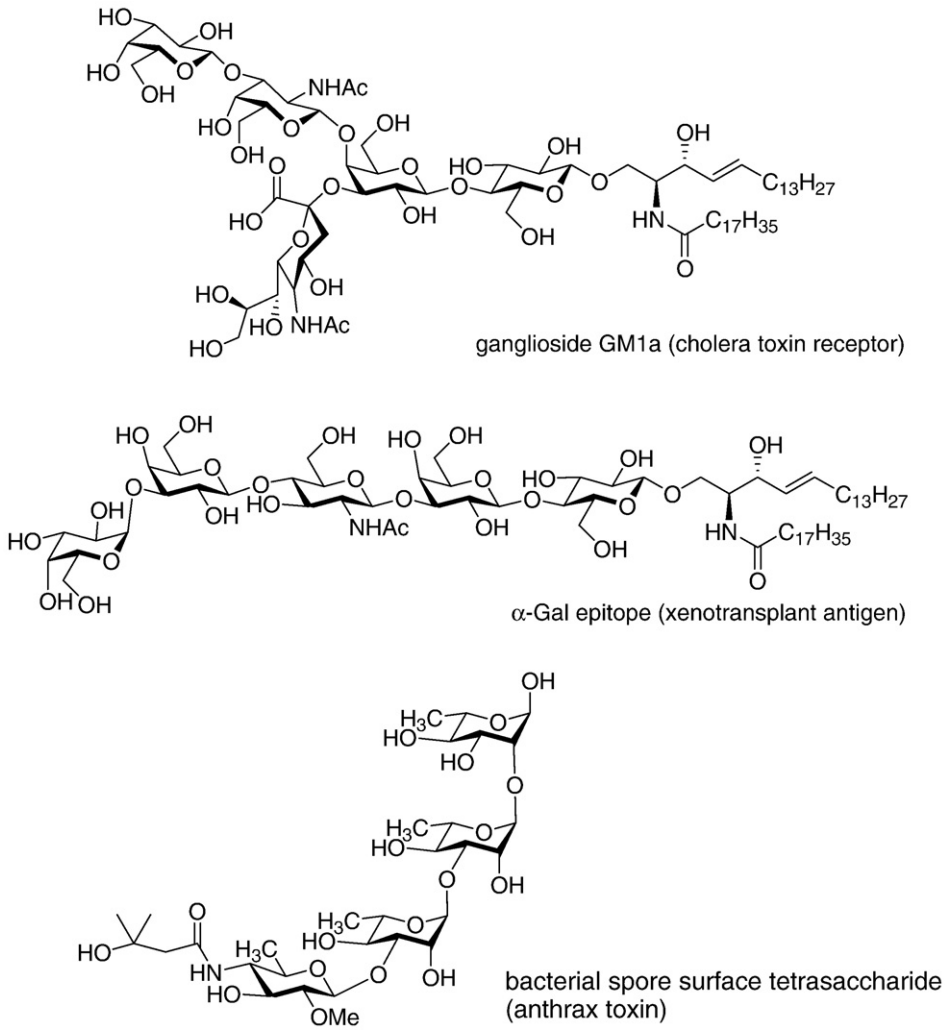

Fig. 1. Examples of bioactive cell-surface oligosaccharides involved in carbohydrate–protein interactions.