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Seeing cellular sialidase transform sugars

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Abstract

Cell-surface carbohydrates are synthesized in a step-wise fashion, yielding products with unique capping structures. A recent study has shown that carbohydrates at the cell surface can be further remodeled by an endogenous glycosidase to alter the carbohydrate structure, thus generating a new function.

Carbohydrates serve important roles in eukaryotic cells, and in particular they function as intercellular regulators when displayed on the cell surface as protein or lipid conjugates. These often complex sugar structures are typically synthesized in the endoplasmic reticulum and Golgi apparatus by the step-wise addition of different carbohydrate residues onto the appropriate biological scaffold by glycosyltransferases. This occurs in the creation of mucin-like O-glycans, which are initiated by the addition of *N*-acetylgalactosamine to serine or threonine residues¹. Unlike DNA and protein synthesis, however, carbohydrate synthesis does not always proceed in a forward direction; instead, individual or several sugar residues can be removed, or ‘trimmed’, from a growing chain while in the endoplasmic reticulum and Golgi. This processing is well known, for example in the case of converting mannose-rich N-glycans to precursor N-glycans in the Golgi by mannosidases, a required step in converting the carbohydrates present in yeast to the more complex N-glycans in animal and plant cells². The significance of appropriate carbohydrate modification is illustrated by neonatal lethality in mice with inactivated α -mannosidases³. A new study now demonstrates a surprising link between these systems in describing a mucin-like sugar epitope modification of existing glycoproteins by a post-Golgi enzymatic activity that underlies myeloid cell maturation and differentiation⁴.

Two particularly important sugars found on the surface of myeloid cells are the CD15 antigen (or Gal- β (1–3)-[Fuc- α (1–3)]-GlcNAc; also known as Lewis x) and its sialylated analog, sialyl-CD15 (or sialic acid- α (2–3)-Gal- β (1–4)-[Fuc- α (1–3)]-GlcNAc; also known as CD15s or sialyl-Lewis x). These closely related structures have surprisingly different functions: neutrophils—a type of white blood cell in the myeloid lineage—use CD15s-selectin interactions to initiate cell adhesion with endothelial cells as part of the inflammatory response⁵. Once neutrophils have entered subendothelial tissues, the cell surface is altered to display CD15, which does not bind selectin, but instead serves as a ligand for the lectin DC-SIGN on dendritic cells. This pairing is one factor that neutrophils use to initiate dendritic cell maturation⁶; it engages both neutrophils and dendritic cells in attacking pathogens.

Though the functional significance of the display of either CD15s or CD15 is clear, the mechanism controlling which sugar is displayed was not known. The replacement of CD15s could result from vigorous new synthesis of CD15, thus diluting CD15s. Alternatively, CD15s

could be directly digested by an endogenous sialidase and converted to CD15 through a new mechanism. Gadhoom and Sackstein now use inhibitors of specific points in carbohydrate synthesis to show that CD15 is surprisingly generated by the latter mechanism⁴ (Fig. 1). Even more surprisingly, by measuring the sialidase activity of intact cells, the authors show that the majority, if not all, of the sialidase activity that cleaves CD15s is present on the cell surface.

To remove sialic acid from the cell surface, four distinct sialidases reported are considered⁷. Among them, only Neu-1 and Neu-3 can hydrolyze sialic acid conjugate. Gadhoom and Sackstein showed that Neu-1 is most likely responsible for the conversion of CD15s to CD15 by demonstrating that the levels of its transcripts and protein were increased during differentiation of myeloid cells. Gadhoom and Sackstein also showed that the majority of CD15 expressed in differentiated neutrophils is present on two glycoproteins: CD43 and PSGL-1. This is a rather surprising finding given that CD15 is abundantly present in glycolipids⁸. Considering that CD43 and PSGL-1 are extended from the plasma membrane, it is important to determine how Neu-1 reaches the end of such extended molecules.

The conversion of CD15s to CD15 may also have significance in differentiation and maturation of other hematopoietic cells. Neutrophil progenitor cells are thought to adhere to bone marrow stroma probably using a CD15s–PSGL-1 interaction⁹. Similarly, immature T lymphocytes bind to thymus stroma cells through interaction of CD15s and PSGL-1 (ref. 10). Differentiation and maturation of these progenitor cells and immature cells may also be associated with switching of adhesive counterparts through removing sialic acid by endogenous sialidase. In another exemplary system, the B-cell-specific lectin CD22 binds to α (2–6)-linked sialic acid, and B-cells deficient in the enzyme that forms α (2–6)-linked sialic acid show suppressed B-cell receptor complex signaling^{11,12}. It is possible that endogenous sialidase removes this terminal sialic acid and thereby regulates B-cell receptor complex-mediated signaling. The work by Gadhoom and Sackstein shows that these and perhaps other novel functions of endogenous sialidase are yet to be explored.

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■ GalNAc
 ■ GlcNAc
 ● Gal
 ◆ Sialic acid
 ▲ Fuc

Figure 1.

Biosynthetic pathway of mucin-like O-glycans. Once mucin-type O-glycans are synthesized in the Golgi by glycosyltransferases (GTs), the corresponding mucin-like glycoproteins are transported to the plasma membrane. Gadhoum and Sackstein showed that CD15s (sLe^x) on mucin-type glycoproteins is further subjected to processing by an endogenous sialidase on the cell surface, thus forming CD15 (Le^x). Proteins are shown in light blue.