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Review

Getting a handle on glycogen synthase – Its interaction with glycogenin

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ABSTRACT

Glycogen is a polymer of glucose that serves as a major energy reserve in eukaryotes. It is synthesized through the cooperative action of glycogen synthase (GS), glycogenin (GN) and glycogen branching enzyme. GN initiates the first enzymatic step in the glycogen synthesis process by self glucosylation of a short 8–12 glucose residue primer. After interacting with GN, GS then extends this sugar primer to form glycogen particles of different sizes. We discuss recent developments in the structural biology characterization of GS and GN enzymes, which have contributed to a better understanding of how the two proteins interact and how they collaborate to synthesize glycogen particles.

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1. Introduction

Glycogen is a branched polymer of glucose joined through an α1,4 glycosidic linkage with intersecting α1,6 linked glucose residues that serve as branch points. Glycogen is synthesized through cooperative actions of glycogen synthase (GS), glycogenin (GN) and glycogen branching enzyme (GBE) (Roach, 2002). GN sits at the core of the glycogen particle (Whelan, 1986) and initiates the process of particle formation by first transferring glucose residues onto itself, leading to an α-1,4 linked chain of 8-12 glucose units (Pitcher et al., 1987). The resulting oligosaccharide, still attached to GN, serves as the primer that is converted into a full-size glycogen particle through the combined action of GS and GBE (Roach, 2002).

Below we provide a brief review of the structural features of GS and GN and how these two enzymes interact to initiate glycogen biogenesis.

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2. Glycogenin is an autoglucosylating dimer

Humans contain two tissue specific GN isoforms. GN1 is expressed ubiquitously but found predominantly in muscle, whereas GN2 is expressed specifically in liver. GN contains a conserved Rossmann fold domain of approximately 250 amino acids at its N-terminus that is required for uridine diphosphate glucose (UDP-G) binding and catalysis. Additionally, GN also contains a highly conserved region of 30–35 residues at its C-terminus that is sufficient and required for binding to GS (Fig. 1A). The N-terminal Rossmann fold domain and the conserved C-terminal region of GN are connected by a linker region that is not conserved in either length or amino acid composition across various species and isoforms (Fig. 1A). This linker varies in length from 2–3 residues in *C. elegans* CeGN-b isoform (Uniprot ID H2KYQ5-2; generated through alternative splicing) to ~250 in *S. cerevisiae* ScGN1 (Uniprot ID P36143 (Fig. 1A)), and its precise function is unknown.

GN (EC 2.4.1.186) also has a glycosyl transferase A (GT-A) fold with glycosyltransferase (GT) activity. GN belongs to the GT-8 family of glycosyl transferases. A Mn^{2+} ion is required in the active site and plays the role of a Lewis acid catalyst that facilitates leaving group departure (Lairson et al., 2008).

The first structural analysis of rabbit muscle GN revealed a tight homo-dimer with approximately 1300 $Å^2$ of buried surface area (Fig. 2A) (Gibbons et al., 2002). Within the GN dimer, the autoglucosylated tyrosine residue is present in a flexible region and is within reach of the active site of both GN protomers (i.e. a glucose chain can be extended in an intersubunit and intrasubunit manner). Glucose chains of various lengths and number of UDP and Mg^{2+} ions have been solved in GN crystal structures. The structural snapshots of GN catalytic cycles have shown that the first four glucose residues can be added and accommodated by the same catalytic GN protomer in an intrasubunit reaction, but catalysis of longer glucose chains requires the catalytic action of the opposing GN protomer in an intersubunit reaction (Chaikuad et al., 2011).

Interestingly, even in crystals of full length GN, no electron density has been observed for the variable linker region or the conserved C-terminal region that mediates interaction with GS, suggesting that both are disordered in the absence of interacting partners.

3. GS forms a tetramer regulated by G6P binding

GS contains two tandem Rossmann fold domains flanked by N- and C-terminal regulatory regions that contain phosphorylation sites (Fig. 1B). GS has a GT-B fold and belongs to the GT-3 family of glycosyl transferases. Like all eukaryotic GT-3 enzymes, GS is inhibited by protein phosphorylation and activated by binding to glucose 6-phosphate (G6P). Like GN, GS also uses UDP-G as the nucleotide-sugar donor and is a retaining enzyme that catalyzes extension of α1,4-linked oligosaccharides. However, unlike GN, GS does not require the presence of divalent metal ions for catalysis.

Despite the importance and intense interest surrounding GS, its structure was not solved until 2010 when Baskaran et al. reported structures of yeast GS in the presence and absence of the allosteric activator G6P (Baskaran et al., 2010). The GT-B fold is conserved between

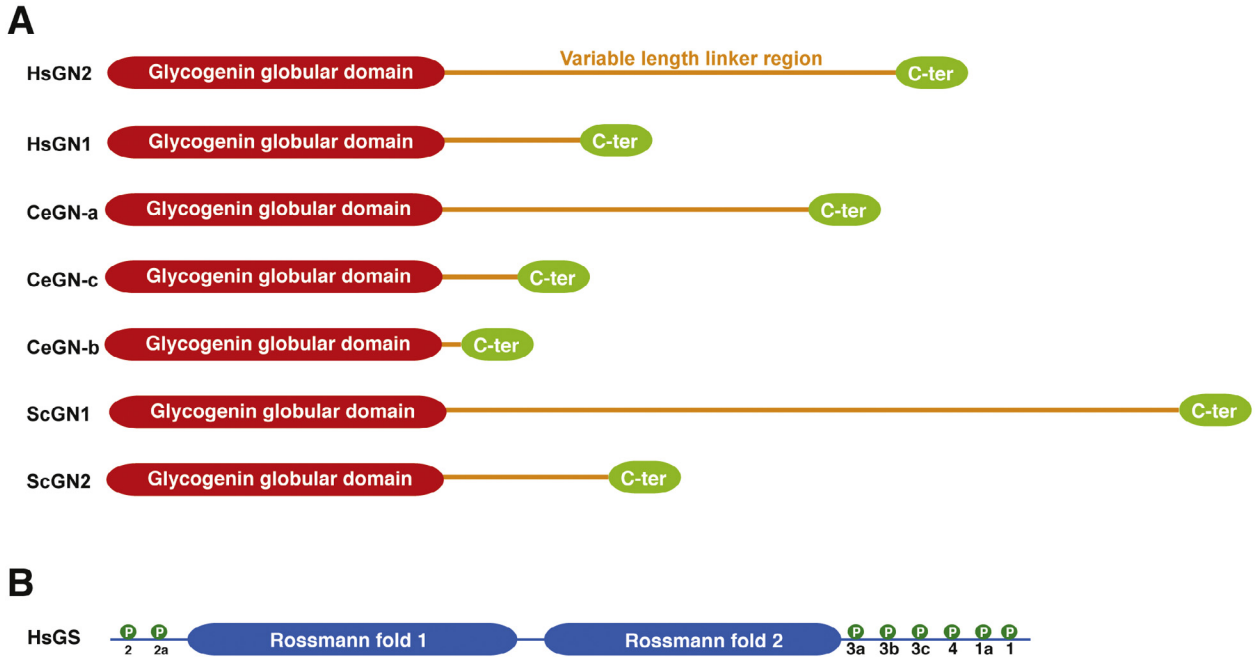

Fig. 1. Domain architecture of glycogenin (GN) and glycogen synthase (GS). (A) Domain architecture of GN from different species. In the case of CeGN three different splice variants are shown. Hs = *H. Sapiens*, Ce = *C. elegans*, Sc = *S. cerevisiae*. (B) Domain architecture of HsGS. Sites of regulatory phosphorylation sites (P) are shown in green.