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The conformational plasticity of glycosyltransferases

David Albesa-Jové [1,2,3,4] and Marcelo E Guerin [1,2,3,4]

Glycosyltransferases (GTs) catalyze the transfer of a sugar moiety from nucleotide-sugar or lipid-phospho-sugar donors to a broad range of acceptor substrates, generating a significant amount of structural diversity in biological systems. GTs are highly selective in nature, allowing the recognition of subtle structural differences in the sequences and stereochemistry of their sugar and acceptor substrates. To achieve the enzyme-transition state complex, a particular spatial arrangement of the active site is required, highlighting the importance of protein dynamics, conformational changes and plasticity of GTs during substrate recognition and catalysis. The elucidations of the molecular mechanisms by which these events govern the function and substrate specificity of GTs represent a major challenge.

Addresses
[1] Structural Biology Unit, CIC bioGUNE, Bizkaia Technology Park, 48160 Derio, Spain
[2] Unidad de Biofísica, Centro Mixto Consejo Superior de Investigaciones Científicas, Universidad del País Vasco/Euskal Herriko Unibertsitatea (CSIC, UPV/EHU), Barrio Sarriena s/n, Leioa, Bizkaia 48940, Spain
[3] Departamento de Bioquímica, Universidad del País Vasco, Leioa, Bizkaia 48940, Spain
[4] IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain

Corresponding author: Guerin, Marcelo E (mrcguerin@cicbiogune.es)

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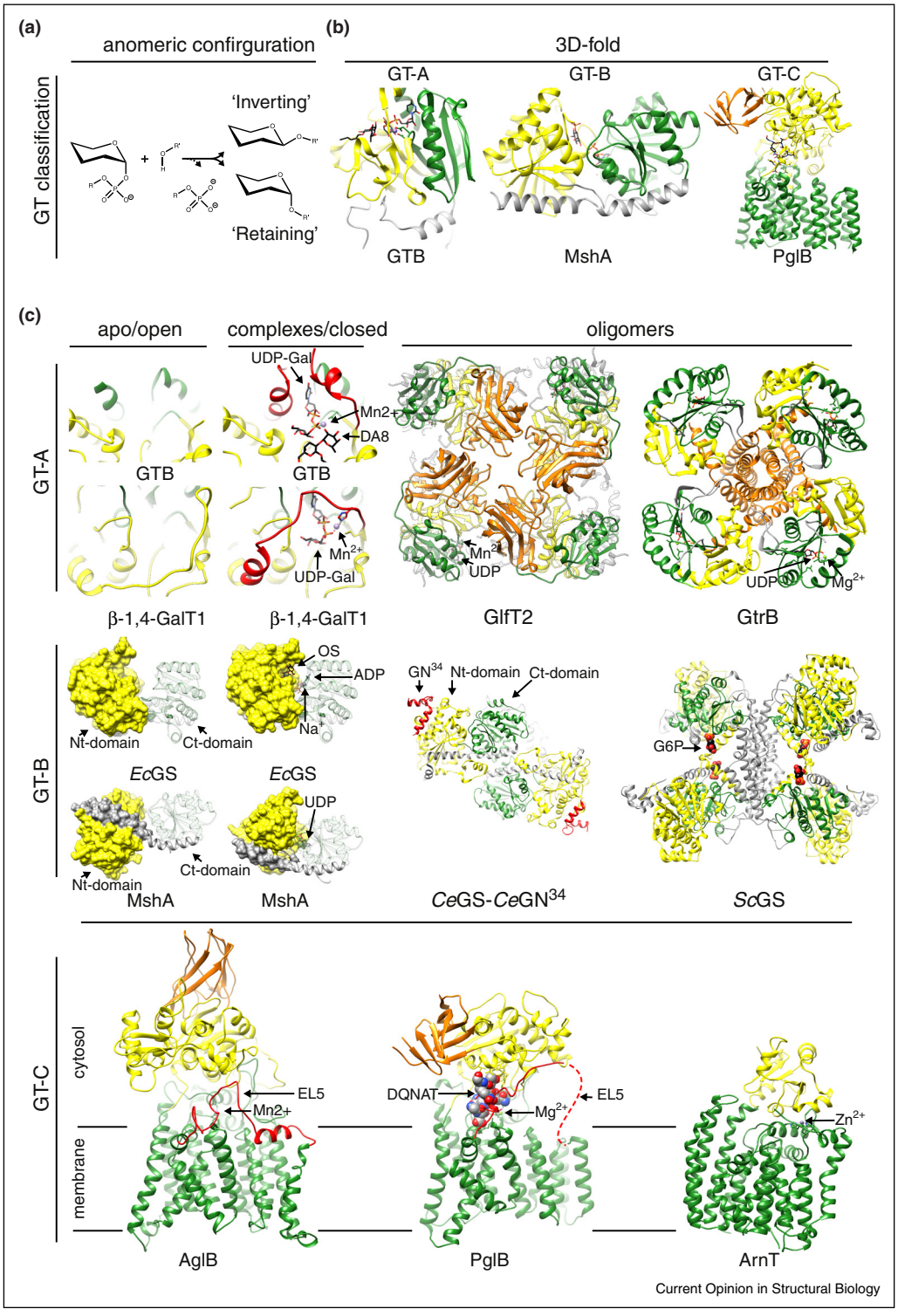
Introduction

Substrate specificity is a fundamental property of enzyme catalysis. Enzymes are characterized by their exceptional capacity to efficiently catalyze a great number of stereospecific chemical reactions in all living organisms. A selective binding and stabilization of the transition state rather than more stable forms of substrates seems to be the major determinant of the chemical reaction step. To achieve such enzyme-transition state complex, a particular spatial arrangement of the active site is required, highlighting the importance of protein dynamics and conformational changes in substrate recognition and catalysis [1,2]. Specifically, protein conformational changes not only involve local reorganization of flexible loops and side-chain residues, but also, in many cases, domain motions and protein oligomerization events. In addition, as a consequence of protein–protein interactions, post-translational modifications, and non-covalent associations with small-molecule inhibitors or activators, protein dynamics critically modulate enzyme catalysis [3,4]. Thus, the elucidations of the molecular mechanisms by which these events modulate the function and substrate specificity of enzymes represent a major challenge.

Here we focused in glycosyltransferases (GTs), a prominent family of enzymes that catalyze the transfer of a sugar moiety from nucleotide-sugar or lipid-phospho-sugar donors to a broad range of acceptor substrates, including monosaccharides, oligosaccharides and polysaccharides, lipids, proteins, nucleic acids and small organic molecules [5]. GTs account for about 1–2% of the gene products of an organism, including archaea, bacteria, or eukaryotes. GTs are highly selective in nature, allowing the recognition of subtle structural differences in the sequences and stereochemistry of their sugar substrates. In that sense, according to the anomeric configuration of reactants and products, GTs are classified in 'inverting' or 'retaining' enzymes (Figure 1a; [5]). GTs have also been distinguished based on amino acid sequence similarities in 98 different families (CAZy database, http://www.cazy.org/; see supplementary content; [6,7]). Interestingly, only three structural folds have been described among the first 42 families for which three-dimensional structures have been reported (Figure 1b). The GT-A and GT-B topologies are variations of Rossmann fold domains, and employ nucleoside diphosphate activated sugars as donors [7]. GT-A enzymes consist of two tightly bound β/α/β Rossmann-fold domains, where the N-terminal domain recognizes the nucleotide sugar donor and the C-terminal domain of the protein contains the acceptor binding site. Most GT-A enzymes display an Asp-X-Asp signature in which the side chain carboxylates coordinate a divalent cation and/or a ribose. However, the Asp-X-Asp signature is not a conserved motif since (i) none of the Asp residues is invariant, (ii) examples do exist of GT-A enzymes lacking the Asp-X-Asp signature, and (iii) many enzymes display an Asp-X-Asp amino acid sequence signature, but are not GTs (Figure 1b; [5]). GT-B enzymes comprise two β/α/β Rossmann-fold domains separated by a large cleft that contains the reaction center. Thus, an important interdomain movement has been predicted/demonstrated in several members of this superfamily during substrate binding and catalysis [5,7]. In GT-B enzymes, the N-terminal domain is involved in acceptor substrate recognition whereas the nucleotide-sugar donors mainly bind to the C-terminal domain. Since acceptors

Figure 1



GTs display a high level of plasticity. **(a)** GT enzymes are classified in 'retaining' or 'inverting' depending of the anomeric configuration of reactants and products. **(b)** Although GTs are found in all domains of life, only three structural folds have been observed, namely GT-A, GT-B and GT-C. **(c)** Protein dynamics and conformational changes play essential roles during substrate recognition independently of enzyme fold. Illustrated GT-A fold includes: GTB (pdb codes 2RIT, 2RJ7), β-(1→4)-galactosyltransferase-1 (β-(1→4)-GalT1 (pdb codes 1PZT, 1O0R), polymerizing GlfT2 (pdb code 4FIY) and GtrB (pdb code 5EKE). Illustrated GT-B fold includes: mycothiol synthase A (MshA; pdb codes 3C4V, 3C48), *Escherichia coli* GS (pdb codes 3D1J, 3CX4), *Caenorhabditis elegans* GS (pdb code 4QLB) and *Saccharomyces cerevisiae* GS (pdb code 3NB0). Illustrated GT-C fold includes: PglB (pdb code 3RCE), archaeal OST (pdb code 3WAK) and ArnT (pdb code 5EZM).