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Commentary

Discovery of Targeted Glycan-Binding Proteins: Approaches and Mechanisms

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DESCRIPTION

Glycan-Binding Protein (GBP) is the proteins that can bind certain glycan sequences, allowing cellular functions to be facilitated based on the glycomic profile. By virtue of their mass, shape, charge, or other physical qualities, glycans can mediate a wide range of biological functions. Many of the biological functions are mediated through GBP recognition. Nature appears to have made the most of the great diversity of glycans expressed in organisms by producing protein modules that can detect discrete glycans that mediate certain physiological or pathological activities. With the exception of glycan-specific antibodies, GBPs can be divided into two categories: Lectins and glycosaminoglycan-binding proteins.

Most lectins belong to families with well-defined "Carbohydrate-Recognition Domains" (CRDs), which appear to have developed from shared ancestral genes and typically maintain distinctive primary amino acid sequence or three-dimensional structure properties. By scanning protein sequence or structural databases, new members of the family can be discovered. Despite this ability to predict novel GBPs, the structures of glycans identified by members of the same lectin family might vary greatly. Many lectins have low single-site binding affinities (Kd values in the micromolar range), whereas certain lectins have substantially higher affinity for glycans (with Kd values in the nanomolar range). Multivalent interactions between numerous CRDs and various glycans are frequently required for those lectins with low affinity to create the high binding interactions that are important in vivo. Specific terminal features of glycan chains are recognized by lectins by fitting them into shallow but well-defined binding spaces. Protein interactions with sulfated glycosaminoglycans, on the other hand, appear to be mediated by surface clusters of positively charged amino acids that align with interior areas of extended anionic glycosaminoglycan chains.

Despite the fact that the structural patterns recognized by a given molecule can be extremely precise, most glycosaminoglycan-binding proteins do not appear to be evolutionarily related. Rather, convergent evolution appears to have produced its defining trait (the ability to detect sulfated glycosaminoglycans). Hyaluronan-binding proteins (hyaladherins) are an exception, with an evolutionarily conserved shape that bind to the short hyaluronan chain segment. The fact that hyaluronan is a nonsulfated glycosaminoglycan, hyaladherins are more closely related to lectins than to other glycosaminoglycan-binding proteins.

From a functional standpoint, GBPs can be divided into two categories: Soluble and membrane-bound. GBPs that are bound to the cell membrane are more likely to be engaged in endocytosis, cell adhesion, or cell signalling, and to remain restricted to the cell type in which they were synthesized. Soluble GBPs, on the other hand, have the ability to diffuse locally in tissues and/or reach the bloodstream. This form of physical classification is beneficial in terms of function, is confused by two issues: For some of the GBPs that start off as membrane-bound proteins can be lost into the extracellular fluid by proteolysis. Second, through their glycan-binding sites, soluble GBPs can bind to cell surfaces or matrices. Some instances of these associations, as well as the type of possible interactions with natural ligands, which can be soluble or membrane-bound.

Glycan-Protein interactions are a type of bimolecular interaction that occurs between glycans and their corresponding binding partners, whether they are free or coupled to proteins. Glycans and proteins to which they are covalently linked have intermolecular glycan-protein (protein-glycan) interactions. They constitute a molecular basis for many key cell functions, particularly cell-cell and host-cell interactions, when combined with protein-protein interactions. For example, SARS-CoV-2, the COVID-19 causal agent, uses it's heavily glycosylated spike protein to connect to the ACE2 receptor and enter host cells. The spike protein is a trimetric structure with 22 N-glycosylation sites in each subunit, which makes it a promising vaccination candidate. Glycan-protein interactions sheds light on the mechanisms of cell signalling and enables for the development of improved diagnostic tools for a variety of disorders, including cancer. Indeed, there are no known cancers that do not entail unpredictable protein glycosylation patterns.

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