Essentials of Glycobiology

Lecture 43

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Course Overview & Summary

"Universal" Principles of Glycobiology: Glycan Occurrence

- All cells in nature are covered with a dense and complex array of carbohydrate chains(glycans)
- Most secreted proteins of eukaryotes also carry large amounts of covalently attached glycans .
- In eukaryotes, these cell surface and secreted glycans are assembled via the ER-Golgi pathway

"Universal" Principles of Glycobiology: Glycan Occurrence

- The extracellular matrix of eukaryotes is also very rich in glycans that are secreted via the same pathway
- Cytosolic and nuclear glycans are also common in eukaryotes
- For topological, evolutionary and biophysical reasons, there is little similarity between cell surface/secreted and nuclear/ cytosolic glycans .

Universal Principles of Glycobiology : Glycan Biosynthesis

- The primary units of glycans (monosaccharides) can be synthesized within a cell or salvaged from the environment
- Monosaccharides must be activated into sugar nucleotides before they are used as donors for glycosyltransferases . Topological barriers are relevant.
- Each linkage unit is assembled by one or more unique glycosyltransferases

"Universal" Principles of Glycobiology: Glycan Biosynthesis

- Many glycosyltransferases are members of multigene families with related functions
- Most glycosyltransferases recognize the underlying glycan substrate, but some are protein-specific
- Many glycosyltransferases are expressed in a tissue-specific, temporally regulated manner

"Universal" Principles of Glycobiology: Glycan Diversity

- Monosaccharides have the potential for far greater combinatorial diversity than nucleotides or amino acids
- Further diversity can arise from covalent modifications of glycans
- Only a limited subset of the potential diversity is found in a given organism or cell type.
- However, there is intrinsic diversity (microheterogeniety) within a given cell type or even a single glycosylation site

"Universal" Principles of Glycobiology: Glycan Diversity

- The glycan repertoire (glycome) of a given cell-type or organism is thus many orders of magnitude more complex than the genome or the proteome
- The glycan repertoire (glycome) of a given cell-type or organism is also highly dynamic, responding to intrinsic and extrinsic signals by under going rapid changes
- Glycome diversity in species, space and time can help explain why there are only a limited number of genes in the typical genome

"Universal" Principles of Glycobiology: Glycan Recognition

- Glycans can be recognized by many specific-binding proteins intrinsic to the organism synthesizing the glycans
- Glycans are also recognized by many binding proteins of pathogens and symbionts
- Glycan -recognizing proteins often show a high degree of stereospecificity for binding to specific glycan structures, but typically have relatively low affinities for single site binding

"Universal" Principles of Glycobiology: Glycan Recognition

- Thus, biologically relevant recognition usually requires multivalency of glycan and receptor, in order to generate high avidity of binding
- Glycan-recognizing proteins fall into two categories: those with common evolutionary origins (e.g., lectins) and those that have evolved by convergent evolution (e.g, GAG binding proteins)

"Universal" Principles of Glycobiology: Glycan Genetics

- Naturally occurring genetic defects in cell surface/secreted glycans seem relatively rare in intact organisms. However, this may be due to an ascertainment bias caused by unpredictable or pleiotropic phenotypes
- Genetic defects in cell surface/secreted glycans are easily obtained in cultured cells, but have somewhat limited biological consequences

"Universal" Principles of Glycobiology: Glycan Genetics

- The same mutations typically have major phenotypic consequences in an intact multicellular organism
- This implies that many of the major roles of cell surface/secreted glycans involve cell-cell or extracellular interactions
- Nuclear/ cytosolic glycans may play more cell-intrinsic roles e.g., in signalling .

"Universal" Principles of Glycobiology: Glycan Roles

- Biological roles for glycans span the spectrum from non-essential activities to those that are crucial for the development, function and survival of an organism
- All of the theories regarding the biological roles of glycans appear to be correct, but exceptions to each can be found
- Glycans can play different roles in different tissues, or at different times in development

"Universal" Principles of Glycobiology : Glycan Roles

- Terminal sequences, unusual glycans, and modifications are more likely to mediate specific biological roles
- However, unusual glycans or modifications might also reflect prior evolutionary interactions with microorganisms and other noxious agents
- Thus, *a priori* prediction of the functions of a specific glycan or its relative importance to the organism is difficult

"Universal" Principles of Glycobiology : Evolution

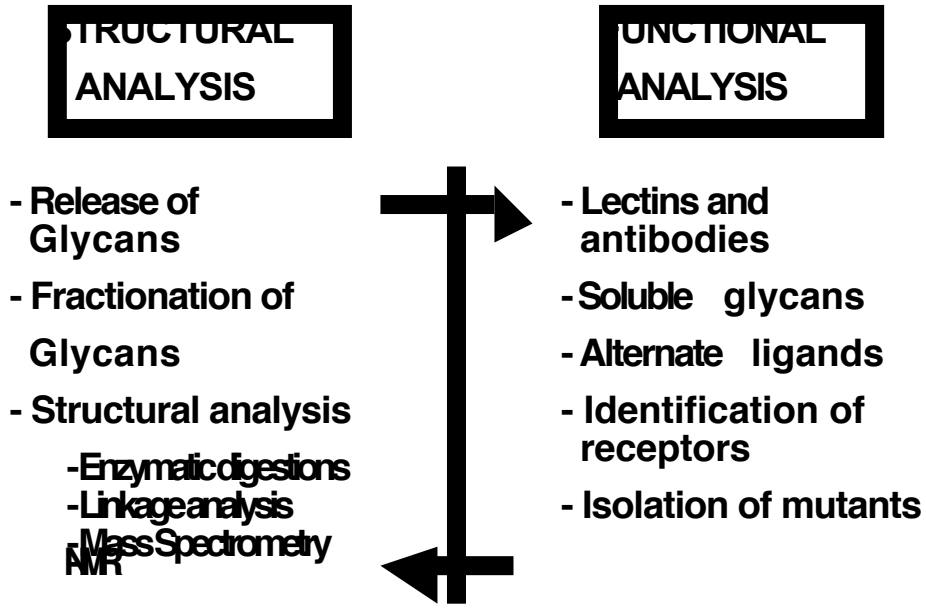
- Relatively little is known about the glycan evolution
- Inter-species and intra-species variations in glycan structure are relatively common, suggesting rapid evolution
- Most likely mechanism for rapid evolution is selection pressure by pathogens than recognize glycans

"Universal" Principles of Glycobiology : Evolution

- However, glycan evolution must also preserve critical intrinsic functions
- Interplay between pathogen selection pressure and preservation of intrinsic roles could also result in the formation of "junk" glycans
- Such "junk" glycans could be the substrate from which new intrinsic functions arise during evolution

Future Perspectives

- Improvements in analytical methods will speed analysis of glycan mixtures
- Improvements in synthetic methods will make available custom glycans in large quantities for therapeutics and as analytical reagents
- Model organisms will continue to grow in utility as genomic initiatives expand and better genetic tools come on-line
- Nutritional and environmental factors will be important in modulating glycan structure and functions


STRUCTURAL ANALYSIS
FUNCTIONAL ANALYSIS
- Release of Glycans
- Fractionation of Glycans
- Structural analysis
-Enzymatic digestions
-Linkage analysis
-Mass Spectrometry
-NMR
- Lectins and antibodies
- Soluble glycans
- Alternate ligands
- Identification of receptors
- Isolation of mutants