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Editorial

Metabolic bioengineering: glycans and glycoconjugates

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The application of metabolic engineering to the production of glycans and glycoconjugates is the subject of the current special issue of *Emerging Topics in Life Science*. The lack of availability of these complex carbohydrate or saccharide structures has severely limited the development of the field of glycobiology. This issue contains eight articles from respected scientists in the field that cover this new and emerging field.

Metabolic engineering while still a young field has made remarkable advances in using cellular engineering to produce natural products having molecular mass of under 1000 Da. The fundamental question metabolic engineering is trying to address what are the genetic modifications that will result in an improved phenotype, which is usually associated with the overproduction of a chemical of interest. For more than 20 years, metabolic engineering has successfully resulted in the establishment of mostly microbial production platforms for various chemicals, such as biofuels, pharmaceuticals, and nutraceuticals, resulting in enormous environmental, economic, and societal impacts [1].

Glycans are carbohydrates ranging from simple monosaccharides or disaccharides, such as glucose and lactose, to structurally complex oligosaccharides and polysaccharides. Glycans, part of the metabolome, are synthesized by both prokaryotes and eukaryotes as energy molecules, structural molecules, and informational molecules [2]. Glycoconjugates are glycans that are conjugated to other natural products, such as small aglycones or lipids, or biopolymers, such as proteins or nucleic acids. Glycans and glycoconjugates are generally hydrophilic and highly chiral molecules that are difficult to both synthesize and analyze. Small structural differences in glycans and glycoconjugates can have a profound functional impact on the biology of these molecules. The glycome of an organism represents the most complex portion of its metabolome and is many orders of magnitude more complex than its genome or proteome. Moreover, while one gene typically affords a single protein product, there is not a simple one-to-one correspondence between either the genome or the proteome and the glycome. In eukaryotes, complex glycans and glycoconjugates are generally synthesized through biosynthetic pathways in the Golgi. While many of the enzymes involved in these pathways are known, there is little understanding of the control and regulation of glycan biosynthesis.

Metabolic engineering holds a great deal of promise for the bioengineering of glycans and glycoconjugates in both prokaryotes and eukaryotes. The metabolic engineering of prokaryotes offers the opportunity to prepare high-value sugar-based chemicals, biochemical, nutracueticals, and pharmaceuticals from simple feedstocks ranging from carbon dioxide, to glycerol to glucose. More recent advances in the metabolic engineering of eukaryotes suggest an opportunity to engineer structurally complex glycoconjugates as high-value therapeutics or vaccines and also for the production of novel cell types for tissue engineering and regenerative medicine.

This issue of *Emerging Topics in Life Sciences* is to our knowledge the first thematic issue of a scientific journal dedicated to the metabolic engineering of glycans and glycoconjugates. The articles contained within cover a wide range of carbohydrate-target structures and describe a variety of metabolic engineering strategies. The reviews presented in this issue are summarized below

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Summary

- *Metabolic engineering of capsular polysaccharides* — Capsular polysaccharides (CPS) are found in bacteria as part of the cell wall or surrounding the bacterial cell. Their metabolic engineering (ME) can serve as a source of CPS for vaccines or can be further modified to afford more valuable compounds. The pathways of CPS biosynthesis as well as ME for the preparation of heparosan, chondroitin, hyaluronan, and polysialic acid are discussed.

- *Microbial production and metabolic engineering of chondroitin and chondroitin sulfate* — Chondroitin sulfate (CS) is an important nutraceutical and pharmaceutical polysaccharide. The chondroitin backbone can be made through ME of bacteria-producing CPS and then modified through chemical or enzymatic sulfonation to afford CS for various therapeutic applications.

- *Chemical and biological methods for probing structure and functions of polysialic acids* — Polysialic acids (PSAs) are found both as a CPS and also as a side-chain neural cell adhesion molecule (NCAM) in mammals. PSA expression is essential for normal CNS development, learning, memory, and mental health. There are PSAs having different glycosidic linkages. Various genetic and chemical tools are available for the ME of PSAs including the use of *N*-acetyl mannosamine analogs. The applications of these tools to the ME of PSA, for applications ranging from basic biology to medicine, are discussed.

- *Metabolic engineering for the production of chitooligosaccharides: advances and perspectives* — Chitin oligosaccharides (COs) and the structurally related chitosan oligosaccharides have applications ranging from agriculture to pharmaceuticals. While these are often produced through the chemical/enzymatic degradation of insect and crustacean exoskeletons. Chemical and enzymatic synthesis is complex and costly. ME of COs and COSs offers a new and environmentally advantageous and cost-effective approach.

- *Metabolic engineering of glycosylated polyketide biosynthesis* — Many high-value pharmaceuticals are glycosides, sugar-functionalized natural products. While these have been prepared by extraction from plant and animal tissues, such approaches does not allow for the diversification and discovery of new structures. ME of microbes, bacteria, and yeast, for the production of glycosylated plant polyketides, anthrocyanidins, and flavonoids, are discussed.

- *Biosynthesis and metabolic engineering of pseudo-oligosaccharides* — Pseudo-oligosaccharides (PSOs) are microbially derived secondary metabolites with chemical structures containing pseudosugars or glycomimetics. Such PSOs often exhibit biological activities useful in medicine and agriculture. Because of the structural similarity of PSOs to natural sugars, they can have a profound impact on metabolic pathways. The importance of ME for the production of various PSOs is discussed.

- *Metabolic engineering of glycoprotein biosynthesis in bacteria* — Many new drugs are polypeptide- or protein-based and many of these are glycoproteins (GPs). While GPs are primarily prepared by mammalian cell culture, the opportunity for their microbial production in organisms such as *Escherichia coli* could greatly facilitate their production. The challenges of using ME to produce *N*-linked and *O*-linked GPs in bacteria are discussed.

- *Metabolic engineering of CHO cells to prepare glycoproteins* — Chinese hamster ovary (CHO) cells have emerged as the recombinant GP production platform of choice for biopharmaceutical manufacturing. CHO cell glycosylation varies from that of human cells and can have an impact on the efficacy and safety of GP-based drugs. Recent strategies aimed at modulating the *N*-glycosylation profiles for CHO cells, especially for antibody fucosylation and sialylation, are discussed.

- *Metabolic engineering of mammalian cells to produce heparan sulfates* — Heparan sulfates (HSs) are important animal polysaccharides in developmental biology and normal and pathophysiology. Heparin is a highly sulfated HS that is widely used as an anticoagulant drug. The ME of human kidney (HEK293) cells and CHO cells for the production of HSW and heparin is discussed.

Abbreviations

CHO, Chinese hamster ovary; COs, chitin oligosaccharides; CPS, capsular polysaccharides; CS, chondroitin sulfate; GPs, glycoproteins; HS, heparan sulfates; ME, metabolic engineering; PSAs, polysialic acids; PSOs, pseudo-oligosaccharides.

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Competing Interests

The Authors declare that there are no competing interests associated with the manuscript.

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