TKK Young Scientist Award in Chemical Science

Deciphering the Sweet 'Dressing Code' on Cells

By YAN Fusheng (Staff Reporter)

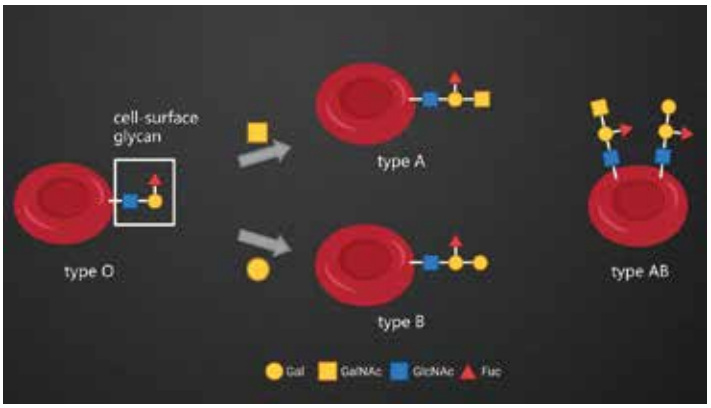
Prof. CHEN Xing
College of Chemistry and Molecular Engineering
Peking University

The 2020 TKK Young Scientist Award in Chemical Science was awarded to CHEN Xing, a professor at Peking University, for his contributions in developing chemical tools for deciphering the biological function of glycans, an important biomacromolecule made of sugars, in cells.

Sugar, a popular substance in daily life, is also loved by cells, which even wear a coat of sugars on their surfaces.

In biological terms, these cell-surface sugars are called cell-surface glycans. Glycans, also termed polysaccharides and sugar chains, are made up of monosaccharides, the smallest sugar units that no long break down to give other sugars. The sugar chains are mostly in branched forms like trees, setting their roots on proteins or lipids dwellings in the cell membrane. Different sugar compositions and arrangements give rise to different forms of trees, like birch or bush, and different cell-surface landscapes, barren or forested.

"This layer of sugars on the cell surface [glycans] not only forms a structural landscape, but also accommodates diverse biological information. The cell can be seen as a forested planet. If you approach this planet from the outer space, it is the forest that you will first make contact with, rather than the ground. In the forest, there grows all kinds of trees, protruding their branches that cover the ground. Just like the trees, cell-surface sugars, are the outermost layer that makes contact with other cells or biomolecules, which shall play important roles in many aspects of life," says CHEN in a public talk.



The four blood types are determined by a set of particular glycans on blood cells. These glycans consist of different monosaccharides, as represented by different shapes and colors. (Image by CHEN's Lab)

For example, a particular set of cell-surface sugars on blood cells determines the blood types – the blood type of A, B, O or AB – which is the first thing needed to be sorted out before conducting a proper blood transfusion. In this case, the cell-surface sugars serve as an identity tag that specifies a cell's identity.

Would bad things happen when a cell is against its proper 'dressing code'?

The answer is YES. Accumulating evidence suggests that abnormal changes on cell-surface sugars are implicated in cancer. However, it was very difficult to get a clearer picture, because studying sugars is not easy.

The central dogma of molecular biology defines the flow of genetic information from DNA to RNA to protein. Based on this principle, lots of techniques have been developed to study and manipulate these molecules.

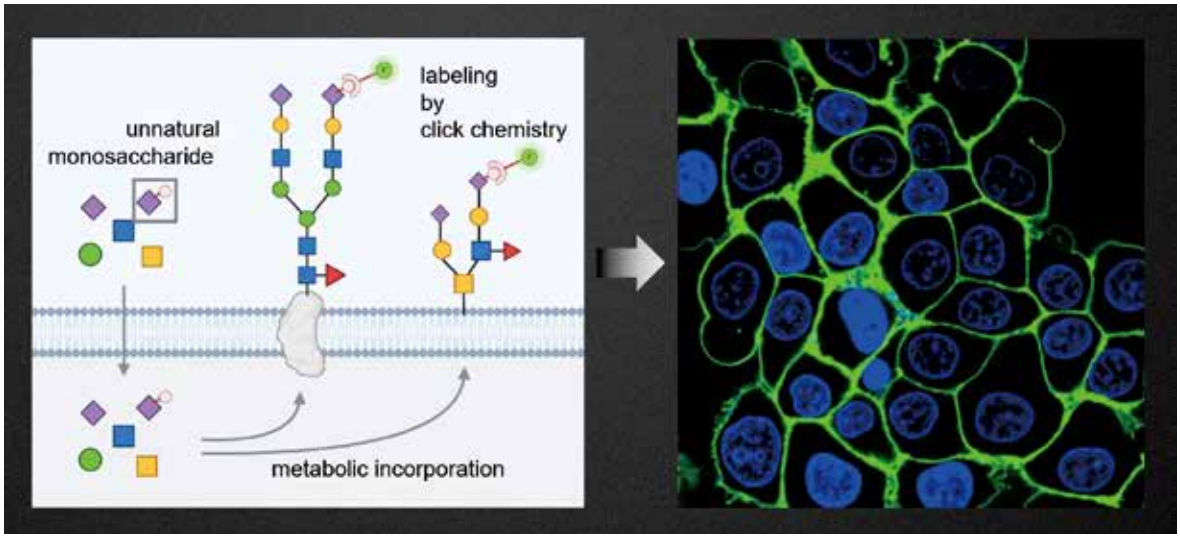
However, sugars are outside of the box of the central dogma. Compared to DNA and proteins, sugars are more like 'street urchins', that are not easy to discipline. Therefore, easy-to-use tools for studying these molecules remain absent for quite a long time. This is also the reason why our understanding of sugars lags behind that of genes or proteins.

With no handy tools available, CHEN has developed his own home-made widgets to chemically label the cell-surface sugars, which subsequently can be studied for various purposes.

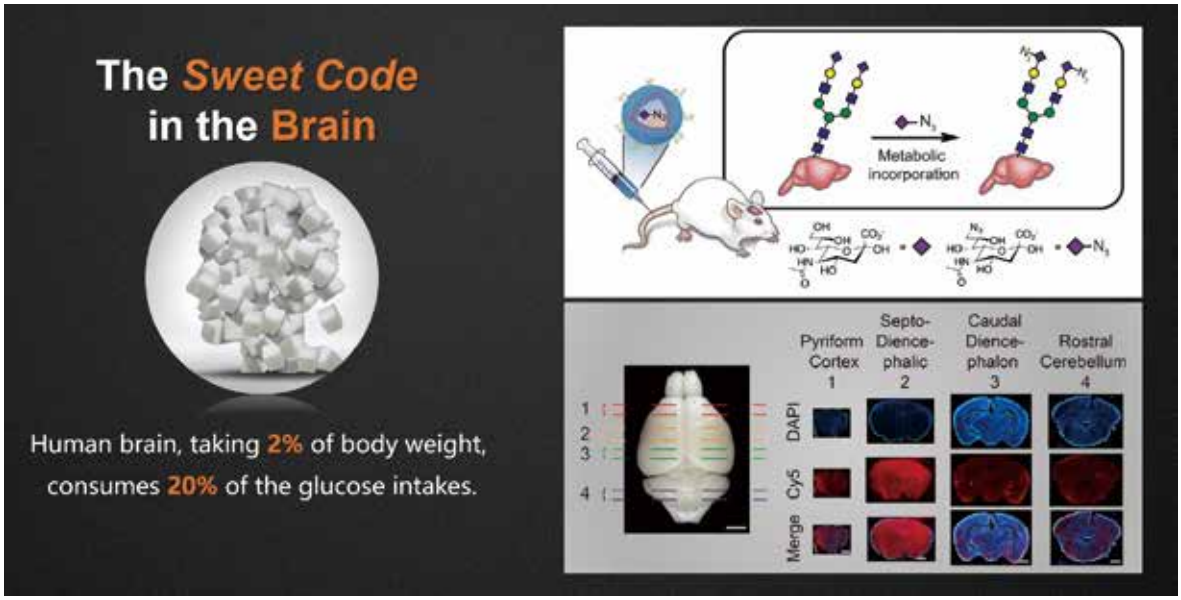
To probe this sugar coat, CHEN's Lab chemically synthesized a plethora of unnatural sugar units (monosaccharide analogs) that can be taken up by cells, metabolically incorporated into sugar chains, and then presented to cell surfaces. By adding a biorthogonal functional group to these unnatural sugar units, one can specifically tag the cell-surface sugars with an imaging probe or an enrichment tag that carries a mutually reactive biorthogonal group. In such so-called 'biorthogonal reactions', the two participating groups are mutually reactive while remaining inert to the surrounding biomolecules, ensuring a superior specificity by only forging bonds with the molecules of interest, in this case, the sugar coat on cells.

CHEN's Lab takes a particularly interest in one type of sugar unit called sialic acid, a family of nine-carbon acidic sugar units, which usually take the terminal position on the branches of the 'tree-like' sugar chain. These acidic sugars are one of the reasons why cells are negatively charged, and the sialylated sugars (sialic acid-containing sugars) are linked with various physiological and pathological events.

Since the unnatural sugars are metabolically added to the growing chains of sugars, only the newly synthesized sugars would host the biorthogonal



Lighting up the cell-surface sugars by metabolic glycan labeling. Unnatural sugar units (monosaccharide analogs) that contain a biorthogonal group are fed to cells, and are thereby metabolically added into the newly synthesized sugars later presented onto the cell surface. When the fluorescent probes that carries the other part of the mutually reactive biorthogonal group are added to the cells, these imaging probes will specifically attach to the unnatural sugars, which resultantly lights up the cell-surface sugars. (Image by CHEN's Lab)



Probing the 'sweet code' in the brain. (Image by CHEN's Lab)

groups. This allows CHEN's Lab to probe the dynamic changes of sialylation during biological events by taking a time series of snapshots of cells that are fluorescently lighted up.

For example, by metabolic labeling of sialylated sugars during epithelial-mesenchymal transition (EMT, a fundamental stage during embryonic development and organogenesis, in which the embryonic cells move actively), they found that cellular sialylation was downregulated during EMT, followed by reversion and upregulation. Consistently, they also observed an enhancement of EMT process by inhibiting cellular synthesis of sialic acid, which resultantly lowers the sialylation level on the cell surface. In most cases, the malignancy of cancers positively correlates with the mobility of cancerous cells, in which the abnormal sialylation may play a role in the dark.

This 'sweet coat of fashion' shall also prevail in the brain, which, taking 2% of body weight, consumes about 20% of the glucose intakes. Considering that the sweet coat is linked with many important errands of a cell, such as 'chatting' with other cells and 'becoming attached' to another cell. The dressing codes for various types of neural cells are thereby supposed to be strictly regulated. When a neural cell fails to maintain a proper dressing code, it may cause problems, such as neurodegenerative diseases.

In an early work using mouse as a model, CHEN's Lab demonstrated the feasibility to probe the distribution of sialylated sugars in different brain zones.

However, what functional roles the cell-surface sugars play in neural connections and in neurodegeneration remains to be explored. By looking at these events with a sweeter perspective, we may acquire new insights into the underlying mechanisms and find some new ways of medical interferences to stop or even reverse the diseases.

The good news is, CHEN's Lab is heading this way.