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Sugar rush

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Once dismissed as mere decoration, sugar molecules turn out to be vital components in life's intricate machinery. Now the race is on to exploit them, says Karen Schmidt

"THEY SAY DNA is the 'Blueprint of Life'. It bloody isn't!" growled one British biologist at a recent debate. Perhaps he was speaking figuratively, but it turns out that he is spot on. For all the fanfare surrounding the unveiling of genome after genome, you could be forgiven for thinking that DNA and proteins are all there is to life.

But there is another code out there to be deciphered - a more subtle, more complex alphabet that spells out the structures of massive molecules that subtly monitor and guide the day-to-day lives of the cells in our bodies. And surprising though it may seem, the letters of this alphabet are made of sugar.

You may think of sugars as simple substances you use to sweeten your coffee. But simple sugars can be built into giant molecules called complex sugars that rival DNA and proteins in size and complexity. Until recently, biologists thought that living things used them either mainly for storing energy, as a structural material (in the form of cellulose, for example) or perhaps as mere decorations on the surfaces of cells. But now it has become clear that these molecules are far more than just the icing on the cake.

It turns out that sugars are involved in almost every aspect of biology, from recognising pathogens, to blood clotting, to enabling sperm to penetrate an ovum. The list of things they are already known to do includes regulating the half-life of hormones in the blood, directing embryonic development, and acting as "address codes" for directing traffic of various cells and proteins throughout the body. Biologists are only just beginning to get to grips with these sugars, but as they do they are finding themselves having to rethink long-held ideas about how life works. "This is going to be the future," declares biochemist Gerald Hart of Johns Hopkins University in Baltimore. "We won't understand immunology, neurology, developmental biology or disease until we get a handle on glycobiology."

It's a testament to the importance of sugars that scientists have granted them an "ome" of their own. Just as the "genome" of a creature refers to its entire set of genes and its "proteome" to its set of proteins, the "glycome" of an organism or cell encompasses all the sugars it makes. Still in its infancy, glycomics is slowly revealing its huge cast of sugar-related characters and their myriad roles. "This really is one of the great frontiers in biochemistry," says Hart. "We are where DNA was in 1950."

Indeed, scientists are saying that glycomics could fuel a revolution in biology to rival that of the human genome. But it's not going to be easy. "If you ask, what is the glycome for a single cell type, it's probably many thousands of times more complex than the genome," says Ajit Varki, director of the Glycobiology Research and Training Center at the University of California, San Diego. "It's going to be a tough business."

Consider the complexity and subtlety of sugars, and it quickly becomes apparent that "tough" is, if anything, an understatement. For a start, the glycome's basic building blocks are far more numerous and varied than the four letters of the DNA alphabet or the score of amino acids that make proteins.

The complex sugar molecules that help make living things tick are all built up from simple sugars, or "monosaccharides" such as glucose, and about 10 others. Two ring-shaped monosaccharide molecules can link together to form a disaccharide, the other main building block of complex sugars. Things are made more complex because there are several different ways for the monosaccharides to link together, which leave the two units angled in different directions.

The problem only gets worse as monosaccharide and disaccharide units link together to form polysaccharides, the chains of sugars which in turn form the giant structures of complex sugars. These massive molecules, which can contain more than 200 units, not only come as long chains, but also as intricately

branched structures that decorate the surfaces of cells like a forest of sugary filigree. It's the three-dimensional shape of these sugars that is key to their functions, such as cell recognition. And there's a further complication: different atoms or groups of atoms may be attached to the basic monosaccharide molecules, subtly changing their properties.

All of this adds up to a massive headache for scientists trying to understand the structures and functions of complex sugars. Do the maths and even a mere six-unit sugar of a kind called a glycosaminoglycan has a staggering 12 billion possible versions. Researchers still have no idea how many of all the possibilities are actually exploited by nature, says Ram Sasisekharan, a bioengineer who leads a multidisciplinary team at the Massachusetts Institute of Technology. "We're still scratching the surface in figuring out which sugars are biologically relevant," he notes.

The inherent complexity of sugars is one reason that glycomics has languished for so long. But another key factor is dogma. Researchers have known for decades that sugars often attach to proteins and lipids, especially on cell surfaces and in the jelly-like matrix between cells. But no one thought these sugars did much. Raymond Dwek, head of the University of Oxford's Glycobiology Institute, who coined the term "glycobiology" in 1988, says that sugars were often dismissed as unimportant, "as just decorations on proteins - people didn't know how to deal with them". They could not have been more wrong. As recent advances in genetics have unfolded, the importance of sugars has become ever more apparent.

Although genes don't code for sugars themselves, in the way they code for proteins, they do code for the enzymes that our bodies use to build the sugars. Studies of these enzymes have opened biologists' eyes to vital roles that sugars play in nature.

A key breakthrough came in the late 1980s, when researchers isolated the first gene for a glycosyl transferase, an enzyme that adds sugars to fats and proteins. The discovery gave scientists the first opportunity to study this process, which is usually called glycoslyation, by manipulating the activity of such enzymes. In 1994, a team led by Jamey Marth at the University of California, San Diego, found that unborn mice in which one glycosylation enzyme had been disabled developed misshapen hearts and died before birth. Marth's lab also found another glycosylation enzyme mutation that causes mice to develop an autoimmune disease resembling the human disease lupus, a condition that results in the body attacking many of its own tissues.

And it's not just mice. People who lack a key sugar on the protein transferrin, which transports iron into cells, develop a host of problems, including delayed mental and physical development, liver problems and abnormal-looking skin. "This brought focus to the idea that perhaps you could get pathology [disease] from variable defects related to adding sugar chains to proteins," explains Hudson Freeze, a researcher at the Burnham Institute in La Jolla, California. Since the mid-1990s, 13 different genetic disorders have been identified and classified as "congenital disorders of glycosylation". Freeze is confident many more are waiting to be discovered.

Even many common diseases have turned out to have a sugar link. First, Dwek's group discovered in the mid-1980s that all people with rheumatoid arthritis have an abnormality in the enzyme that attaches the sugar galactose to an antibody. Nowadays, hardly a month goes by without researchers finding new links between diseases and sugar biology. For instance, in July a group at the University of Iowa reported that sugars missing from a cell-surface protein were to blame for some forms of muscular dystrophy. Meanwhile, a team at Umeå University in Sweden identified a sugar receptor that allows the bacterium *Helicobacter pylori* to infect the stomach lining, causing ulcers and cancer.

Studies of the human genome sequence are backing up this idea of sugars as key players. Fully 1 per cent of our genes encode enzymes that contribute to glycosylation. "Now after the Human Genome Project we see that there are many more of these enzymes than first imagined," says Marth. "We don't think we've identified the whole cast of members yet." To date, several hundred genes for glycosylation have been identified and nearly 50 have been mutated in experiments on mice.

All of this has profoundly changed scientists' view of sugars and their place in the scheme of things. "People now realise that we can't manage without them," says Dwek. This new view convinced the US National Institutes of Health last October to allocate $34 million over five years to the Consortium for Functional Glycomics, an international multidisciplinary group devoted to understanding more about sugar biology in living cells.

This surge of interest in sugars is being helped by much-needed innovations in the tools to study them. Advances in mass spectrometry, for example, are allowing researchers to detect and identify tiny amounts of sugars in the body. This year, Sasisekharan and his team at MIT announced that they had linked mass spectrometry with sophisticated computer analysis to identify a sugar related to the anti-clotting drug heparin that appears to be an important regulator of cell growth. When they tested it in mice they found that one version slowed tumour growth and stopped cancers spreading. The sugar is now being tested as a potential drug (*New Scientist*, 26 January, p 11).

Just as exciting are new chemical techniques for synthesising the sugar molecules that researchers would like to investigate for their biological activity. Until now, the only source of these sugars has been plant or animal tissue, and extracting them has been a tall order, given the scarcity of these molecules. This year, another team at MIT, this one led by chemist Peter Seeberger, unveiled an automated synthesiser that can make chain and branching sugar molecules made of up to 12 units about 100 times faster than was previously possible

They are already putting it to use in the search for a novel type of vaccine against the malaria parasite. Their strategy is to find a substance that primes the body to neutralise the parasite's toxin before it destroys red blood cells. To this end, Seeberger and his team have used their synthesiser to create a sugar nearly identical to one found attached to the *P. falciparum* malaria parasite toxin, in the hope it will trigger the required immune response. "It's an anti-toxin vaccine, which is a new approach," says Seeberger. If it works, it will get around the parasite's nasty habit of dodging its host's immune system.

In just two weeks - compared with 10 months by conventional methods - the chemists made the sugar they were after, which was then injected into mice. Sure enough, up to 75 per cent of the immunised mice survived the deadly effects of the parasite toxin, compared with less than 9 per cent of non-immunised mice. The project has now been taken up in Australia, where Louis Schofield and his colleagues at the Walter and Eliza Hall Institute of Medical Research in Melbourne are testing the vaccine in primates. Meanwhile Seeberger and his team are tinkering with the sugar structure in the hope of making the vaccine even more effective.

But getting to grips with the structures and sequences of individual sugars is only half the battle when it comes to developing sugar-based drugs. For one thing, sugars in the body often come in mixtures of subtly different forms - for instance, one protein may come with 10 slightly different sugars attached to it - and these are nearly impossible to separate using standard techniques. "That can be seen as a challenge or the kiss of death," says Sasisekharan.

It means that each cell in the body is likely to display a family of sugars on its surface with related but slightly different members. What's more, a given cell's glycome can be in a constant state of flux. Cells may be able to make subtle changes to their sugar coats by altering which of these sugars are displayed - in response to pathogens, say, or other environmental changes.

To understand this process, biologists will need to learn how cells make and alter their sugars. So far, they know precious little about how this happens. There is no simple recipe or code for sugars as there is for proteins, for example. Instead, sugars are the products of a somewhat mysterious assembly line of enzymes in the Golgi apparatus - a sort of factory within the cell where the finishing touches get added to newly synthesised proteins. As if this wasn't complicated enough, different sorts of enzymes are used for making different sorts of sugars: the ones that add sugars to the cellular matrix are different from those that add sugars to cell surface proteins.

This daunting intricacy may, however, prove to be a boon for human medicine. By modulating the activity of these enzymes, it may prove possible to turn up or turn down aspects in cell behaviour, rather than simply switching them on and off - rather like using a dimmer in place of a simple switch. "That's harder to study," Varki admits, "but from a therapeutic perspective, we would prefer to use something with subtle effects in humans."

Indeed, that's one reason why glycomics holds such promise for possible new drugs, and why so many pharmaceuticals companies are getting in on the act. Several have sugar-based cancer vaccines undergoing clinical tests. Tumour cells have abnormal sugars on their surfaces, and researchers are using that information to design vaccines that could prime the body to recognise and fight tumour cells more effectively. Samuel Danishefsy and his colleagues at the Sloan-Kettering Institute in New York are designing and testing a vaccine that contains several sugars, increasing the chances that it will provoke a more efficient immune response against cancer cells. He says he expects to know in the next few years if this approach to treating cancer will work.

Other researchers are looking at the role of sugars in bacteria, viruses and other pathogens. These organisms can exploit sugars as a means of overcoming our defences, and understanding how they do this is already giving drug designers a fresh line of attack. For instance, the influenza virus uses an enzyme called glucosidase to free newly made viruses from cell surface sugars. One new drug has already proved successful in shortening a bout of flu by blocking this enzyme, stopping the viruses spreading from cell to cell.

Glycomics could also shore up our dwindling arsenal of effective antibiotics. An antibiotic called vancomycin is already the premier drug against drug-resistant superbugs, and researchers can now make a version that's even more potent in its ability to hinder bacteria in making their sugar coats. "If sugars allow us to get at new targets, we may be able to get around antibiotic resistance," says Laura Kiessling, a chemist at the University of Wisconsin at Madison. Her lab is investigating sugar compounds that alter how bacteria sense food in their environment. Many disease-causing bacteria rely on such cues to tell them if it is a good idea to grow and multiply. Kiessling hopes to develop drugs that will fool

bacteria into behaving as though there were no food around - and so prevent them from causing disease.

In the light of genetics' stunning success, it is tempting to believe that glycomics will have an equally dramatic effect on biology. Maybe it will, but the road promises to be a bumpy one. Even an enthusiast like Hart tends to be sceptical when people claim they will be able to characterise the complete glycome in a cell or organism. "I don't think they'll do it in our lifetime," he says. "If we focus on specific processes, we can handle the complexity. But even then, it's very hard."

Varki sees it as a journey of exploration. "It's like we've just discovered the continent of North America. Now we have to send out scouting parties to find out how big this is, how many people it will take to investigate, and how tough the problem is."

Did sugars make us smart?

One of the most fascinating questions in biology is how human beings came to evolve such large brains. A sugar, or lack of it, may be one of the factors that contributed to this evolutionary leap.

It turns out that, unlike other mammals, our bodies are missing a cell-surface sugar called *N* -glycolylneuraminic acid. It belongs to the family known as sialic acids, which modulate interactions with microbial invaders.

Strangely, it seems that humans are the only mammals known so far to lack the ability to produce it. Ajit Varki of the Glycobiology Research and Training Center in San Diego confirmed in the 1980s that we lack *N* -glycolylneuraminic acid, and has since found the sugar's absence is due to a mutation that disables the enzyme that should make it. Its absence can probably explain why we are more susceptible than chimpanzees and gorillas to certain diseases, including the form of malaria caused by *Plasmodium falciparum* .

But Varki thinks the consequences of this mutation run even deeper. Intriguingly, his team has found that the mutation in the enzyme arose about 2.5 million years ago, long after humans began to walk upright, but before the brain expanded. What's more, in other mammals - pigs, mice, apes, and others - *N* -glycolylneuraminic acid is regulated so that concentrations are kept low in the brain, suggesting that it is somehow detrimental to that organ. Could it be that the complete loss of this sugar in humans triggered the brain development that made us what we are?

That question has yet to be answered. But Varki's team is already trying to disable and to over-express the gene for the enzyme in mice to learn more about the sugar's function and its impact on evolution.

Sugar-coated chips

The sugar rush is spurring the development of the "glyco chip", a new technology that promises to fuel the glycomics revolution and may even lead to tools for detecting bioterrorism.

Modelled on the DNA chip, the glyco chip is a glass slide covered in an array of hundreds of different sugar dots. Each dot is made by sticking a tiny amount of a known sugar to the slide. Researchers can then add mixtures of proteins such as antibodies to the chip to learn which proteins interact with which sugars. The technology promises to help answer basic biological questions, such as how cells alter their surface sugars in response to the environment, as well as helping researchers survey an organism's entire glycome.

The practical applications could be important too, and include diagnosing diseases and detecting bioterrorism threats. Denong Wang of the Columbia Genome Center in New York has made glyco chips with sugars that occur on the surfaces of pathogens. These sugars are like an identification tag for each pathogen, and trigger an immune response in an infected person. "With only a drop of blood, we can ask whether a person has antibodies to any of these pathogens," says Wang.

This technique could help doctors more rapidly identify a mystery illness caused by bioterrorism. Wang also hopes to develop a "reverse" glyco chip to prevent such a disaster in the first place. He's now making chips coated with antibodies that detect such sugars in the environment, with the aim of using them to monitor air and water for specific pathogens, such as anthrax.

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