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How cells communicate

Prof. Valentin Wittmann, professor in the Department of Chemistry at the University of Constance is investigating carbohydrates. At present, his major area of interest is carbohydrate-RNA and carbohydrate-protein interactions, where he is trying to understand the biological functions of complex sugar molecules (glycans).

Prof. Valentin Wittmann with one of his colleagues in his laboratories at the University of Constance (Photo: Keller-Ullrich)

The researchers are using methods from organic chemistry as well as biological test systems. “Our work is halfway between biology and chemistry,” explains Prof. Wittmann. Naturally, chemists are not only interested in how things function, but also in analysis and synthesis methods.

At present, glycobiotechnology is experiencing a second hype; the first wave was back at the beginning of the 1990s. However, back then, the synthesis and analysis methods were not developed to a degree that would have enabled the researchers to deal with this complex topic.

Now, the sugar researchers have received a boost from the latest findings in genetic research. Once the human genome had been deciphered, the researchers were dismayed to find that humans have considerably fewer than 30,000 genes and a simple worm has as many as 20,000 genes. It seems that the genetic level is not complex enough to explain the differences between humans and threadworms. And that is where the sugars enter the scene.

The chemist Prof. Valentin Wittmann focuses on the chemical biology of carbohydrates. (Photo: Keller-Ullrich)

It is estimated that about 50 per cent of all proteins in the body are present in glycosylated form, i.e. as glycoproteins. And these sugar residues are responsible for the regulation of important biological functions. These might be as simple as the solubility of proteins, but can also be highly complex, such as a specific signalling effect in intercellular recognition and communication processes, for example in inflammations. At first, the proteins are synthesized. In nature, this happens in such a way that a DNA matrix is translated into the amino acid sequence of proteins. The sugar residues are subsequently attached to the amino acids. This is what is referred to as post-translational modifications or secondary gene products," explains Professor Wittmann.

The composition of the highly complex polysaccharides (glycans) is regulated by certain organ- and tissue-specific enzymes. Their activity is influenced by a number of different factors. Since the process is not regulated by a matrix, the glycoproteins differ in their sugar structures (microheterogeneity). The glycosylation of proteins is – despite being the most complex – only one type of post-translational modification. Other post-translational modifications are phosphorylation, ubiquitination and a handful of others. Taken together, this leads to a huge increase in the complexity of the genome.

The unbelievable variety of complex glycans is, on the one hand, a prerequisite for the broad spectrum of their biological functions. On the other hand, it represents a huge challenge for the researchers since they cannot be sequenced or amplified in the same way as DNA or proteins, for example. Chemists working on this problem need a lot of patience. The tasks of the glycans are still not completely known. The proportion of sugar seems to be important for the survival of an organism, but it occasionally appears to be dispensable. Prof. Wittmann’s group is, among other things, looking for a method to find out why this is so.

"Protective groups" are necessary

As it is difficult to create sufficient quantities of pure glycans - due to their microheterogeneity - the researchers are instead synthesizing these sugars. But the synthesis of glycans is far from easy. “The chemical synthesis of these complex structures is very complex and it is a hot topic,” said Professor Wittmann explaining that it requires both sugar and protein chemists. The molecules are so complex and so versatile that a doctoral student might have to limit his/her activities to the synthesis of a single glycan. In other words, it takes years to synthesis a single glycan. This is due to the fact that sugars have many functional groups (OH groups), which interact with each other. The chemists have to differentiate these groups so that many steps are required for every single component. In each step, only individual, specific OH groups are allowed to react with each other (regioselectivity). In addition, the newly formed glycosidic bindings must have a specific spatial orientation (stereoselectivity). The synthesis of many glycans is still a huge challenge for chemists. “Certain motives, for example beta-mannosides, are very tricky,” said Prof. Wittmann, explaining that so-called protective groups are required to prevent undesired reactions. These protective groups will at a later stage be enzymatically removed. Sometimes, the researchers use specific enzymes, but these are not always available in order to generate the desired reaction. A smart solution is the so-called ligation reactions, which are so selective that it is possible to avoid using protective groups. These reactions are of huge interest since they can also be carried out in living cells.

Prof. Valentin Wittmann and his team at the University of Constance are investigating the biological function of complex sugar molecules (Photo: Keller-Ullrich)

“The topic is complex but important,” said Prof. Wittmann, referring to the fact that the researchers are focusing on the fundamental question as to how organisms function. The researchers are trying to understand how biochemical processes regulate the most varied functions, including on different levels, such as cell communication. The synthetic chemists can contribute to the understanding of these processes by developing methods and creating compounds for clarifying the reaction and interaction with proteins. The question is: who recognizes sugars and is there a specific code? Particular focus is put on the lectins.

Only a few structures are resolved

Lectins are proteins that are able to recognize and bind glycans. Prof. Wittmann’s research group is investigating the structural prerequisites that are necessary for the recognition of glycans. It often happens that the lectins bind to several sugar structures simultaneously, which makes the binding tighter (multivalence). This of course only works if the sugars are presented at the correct distance to each other. In order to find out more about the correct distance, the Constance chemists are creating a variety of potential sugar structures using combinatorial synthesis and seeing whether they find one that is connected to an interesting lectin.

The Constance researchers started their investigations with plant lectins. They are now working with physiologically important mammalian galectins, which play an important role in cell adhesion, inflammation, immune reactions and the development of cancer. Their exact function is still unknown, however. An important question relates to how lectins interact with their sugars (their ligands) on the molecular level. If a spatial picture of lectins and the bound ligands becomes available, it will be possible to design new, improved ligands on the computer. This improves the synthesis of specific ligands. A method that is highly suited to the clarification of the spatial structure of lectin-ligand complexes is crystal structure analysis. X-ray images and computer modelling produce a spatial picture. Nevertheless, the crystallization of lectins in complexes with multivalent ligands is extraordinarily difficult. Worldwide, only a few such structures have been resolved. The Constance researchers are delighted that they recently succeeded in clarifying such a lectin-ligand complex. Although this is a complex with a plant lectin, the researchers are nevertheless confident that the insights gained can be transferred to physiologically important lectins. The researchers’ goal is to find high-affinity ligands and use them for diagnosis and therapy.

Further development of synthesis methods

The techniques developed by Prof. Wittmann and his team can be applied in numerous areas. For example, lectins are involved in bacterial or viral infections as they are components of cell membranes, i.e. they are located on the surface of bacteria and viruses. They dock to suitable glycans on the surface of the host cell and infect the cell. Influenza viruses also use this mechanism to infect their prey. New drugs might open up new strategies for disarming or for identifying the pathogens.

The Constance researchers are not only focused on potential applications, but also on the further development of synthesis methods such as glycosylation reactions, new ligation reactions or methods for the presentation of carbohydrate chips. New methods can be used to deal with new issues and problems. That is why the close cooperation of chemists and biologists is so important, in particular in interdisciplinary research projects touching common ground between chemistry and biology. The University of Constance realised the importance of this as long as five years ago and established an interdisciplinary life science course, jointly coordinated by the departments of chemistry and biology. Recently, the efforts of the University in this field were rewarded by the Chemical Biology graduate school being granted a place within the German government’s excellence initiative.

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BioLAGO

Further information

Department of Chemistry
University of Constance
Box M 709
78457 Constance
Tel.: +49 (0)7531 88-4572
Fax: +49 (0)7531 88-4573
E-mail: valentin.wittmann(at)uni-konstanz.de