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Patterns matter!

Deciphering the sugar code...

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Not only DNA and proteins, complex sugars also speak their own language/study in JACS

Chitosans are probably the most versatile and promising functional biopolymers. Chitosans can make plants resistant to diseases, promote their growth, and protect them from heat or drought stress. Under chitosan dressings, even large wounds can heal without scars, chitosan nanoparticles can transport drugs across the blood/brain barrier, and chitosans can replace antibiotics in animal fattening as antimicrobial and immunostimulating feed additives. But of course, chitosans are not miracle cures either: there are many different chitosans, and for each application you have to find exactly the right one if it is to work. Unfortunately, we still understand far too little which chitosan has which effect and how the different chitosans unfold their effects. Only when we understand this, when we understand the "language" of chitosan, we can use it in a targeted way. Researchers from Münster have now come a long way towards achieving this goal.

Chitosans are polysaccharides, i.e. complex sugars. They are chains of varying length of a simple sugar called glucosamine; some of these sugar molecules carry an acetic acid molecule, others do not. Chitosans therefore differ in three factors: the chain length and the number and distribution of acetic acid residues along the sugar chain. For about twenty years, chemists have been able to produce chitosans of different chain lengths and with different amounts of acetic acid residues, and biologists have then investigated their biological activities. Thus, an understanding slowly developed of how these two factors influence the antimicrobial or plant-strengthening effect of chitosans. Such well-characterized chitosans, now called second generation chitosans, are currently used as the basis for new chitosan-based products such as the plant biostimulant "Kitostim".

However, Prof. Moerschbacher from the University of Münster, who as the coordinator of a number of European research projects has had a decisive influence on the development of these second-generation chitosans, suspected early on that the third structural factor, the distribution of acetic acid residues along the sugar chain, also plays a decisive role in determining biological activities. However, this hypothesis could not be tested for a long time because the acetic acid residues are randomly distributed in all chemically produced chitosans. As biochemists and biotechnologists, the members of his team have therefore used enzymes for the production of chitosans, i.e. the natural ‘tools’ involved in the biosynthesis of chitosan in chitosan-containing fungi. With their help, they have now succeeded in producing short chitosan chains (so-called oligomers) with a defined arrangement of acetic acid molecules, and tested their bioactivity.

For this test, the researchers used rice cells that they treated with chitosan oligomers to stimulate their immune system. When they used chitosan oligomers consisting of four sugar units (so-called tetramers) carrying only a single acetic acid residue, it was shown that the

tetramer with the acetic acid residue at the first (‘left-most’) sugar unit (the so-called non-reducing end) had a strong immunostimulating effect, while the other three tetramers were less active or inactive. Thus, very clear differences in bioactivity were found between chitosans with the same chain length (4) and the same number of acetic acid residues (1) when they differed in the position of the acetic acid residue. The study, described as a ‘landmark’ by the reviewers, was published in the Journal of the American Chemical Society (JACS).

Outlook

Such a clear dependence of the bioactivity of a complex sugar on its molecular structure has almost never been observed before. The first and to date only example was human heparin, whose anticoagulant effect is based on a certain distribution of sulphuric acid residues along the sugar chain. It is now known that heparin achieves this effect by binding a coagulation factor to this specific binding site, thus inactivating it. And on the basis of this knowledge, it has been possible to develop anticoagulants with precisely dosed effects and without side effects, which are a blessing for e.g. dialysis patients - and a billion-dollar business for the pharmaceutical industry. Of course, the hope now is that the precisely defined chitosans can be used in a similar way to understand how, for example, scar-free wound healing under chitosan dressings can succeed. To this end, Prof. Moerschbacher's research group is already collaborating intensively with dermatologists and other biomedical experts.

Participating institutions and funding

Work on this project began more than ten years ago with the first observations of a Brazilian doctoral student (Talita Honorato), who - financially supported by a sandwich scholarship from the German Academic Exchange Service DAAD and the state of North Rhine-Westphalia - spent eight months researching in the group of Prof. Moerschbacher Her results were taken up by an Indian doctoral student (Malathi Nampally) - supported by a full DAAD doctoral scholarship - in his group. A Master's candidate (Sven Basa), who was supervised by her, then continued the topic in his own doctoral thesis within the European research projects PolyModE and Nano3Bio; he succeeded in elucidating the structure of the bioactive tetramer. He was temporarily supported by an Indian doctoral student (Subha Das), who spent a total of ten months in the research group of Prof. Moerschbacher in the framework of the Indo-German graduate school Molecular and Cellular Glyco-Sciences MCGS of the Universities of Münster and Hyderabad, financially supported by Deutsche Forschungsgemeinschaft DFG and the Indian University Grants Commission UGC. The doctoral students were supported both practically and theoretically by our Lecturer Dr. Nour Eddine El Gueddari, who passed away in 2018, whose scientific dream of deciphering the chitosan code, we have come a decisive step closer with this study.

Original publication

Basa S., M. Nampally, T. Honorato, S. N. Das, A. R. Podile, N. E. El Gueddari & B. M. Moerschbacher (2020) The Pattern of Acetylation Defines the Priming Activity of Chitosan Tetramers. Journal of the American Chemical Society (in press)

Related Links

Original publication in ‘JACS’: https://doi.org/10.1021/jacs.9b11466

research group Bruno M. Moerschbacher: https://www.uni-muenster.de/Biologie.IBBP/agmoerschbacher/index.html

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