Universität Basel

Research Project

Glycocode:towards the structure and function of glycans

Third-party funded project

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Carbohydrates are an essential class of biopolymers and major constituents of the extracellular matrix in all domains of life. Complex biosynthetic pathways take advantage of the tremendous potential of carbohydrates to generate a large number of different polysaccharides or oligosaccharides that serve for a very large number of different functions: they can be structural components of the cell wall (e.g. cellulose or chitin) or mediate diversity of the cell surface (e.g. LPS of Gram-negative bacteria). Glycosylation is the most frequent post-translational modification of eukaryotic proteins and occurs predominantly on secretory proteins, but cytoplasmic glycosylation of proteins can be used to regulate the activity of the modified proteins. It has always been speculated that many different biological functions can be attributed to carbohydrates and indeed, many of them have been confirmed experimentally (Varki, 1993). It is evident that oligosaccharides have the potential to display biological information and that this information can be interpreted by proteins (lectins) that bind specifically to such oligosaccharides structures. However, in contrast to nucleic acids and proteins, only a limited set of tools are available to study the function of carbohydrates at a molecular level. This is predominantly due to the fact that oligosaccharides are not the primary product of the genetic information but rather of complex biosynthetic pathways that take advantage of the high diversity possible in oligosaccharides. In this proposal, three different laboratories with different expertise in carbohydrate science will join forces to develop novel approaches in carbohydrate biology to address the function of oligosaccharides. We will benefit from the newly developed tools that make it possible to generate defined oligosaccharide structures in biological systems. Recently, the process of N- linked protein glycosylation has been discovered in bacteria (Szymanski et al., 1999) and the functional transfer of this process into *E.coli* has made it possible to establish a novel experimental system that allows the production of N-glycoproteins in *E.coli* (Wacker et al., 2002). In a first line of research, we will take advantage of these tools and will use the novel glycophage display system to create a highly efficient *in vitro* glycosylation system of proteins. This system will then be used to generate defined N-glycoproteins that are used, in a second line of research, for the determination of the three-dimensional structure of oligosaccharides in solution by NMR.

Three-dimensional structures are essential for understanding the interactions of lectins with their substrates. We will study different lectin-carbohydrate complexes at a molecular level. These types of studies will reveal the determinants that govern the binding of oligosaccharides to proteins and they will lead to a better understanding of the synthax of the glycocode. This knowledge will be beneficial to many ar-

eas of science, e.g. the development of glycomimetics applicable to modulate therapeutically important physiological functions. In a third line of research, we will then use this know-how to study the role of lectins in a complex biological system: the innate defense of the basidiomycetous fungus *Coprinopsis cinerea* against predators and parasites.

Keywords carbohydrates, polysaccharides, oligosaccharides, glycosylation, N-glycoproteins
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