Researchers apply systems biology and glycomics to study human inflammatory diseases

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An innovative systems biology approach to understanding the carbohydrate structures in cells is leading to new ways to understand how inflammatory illnesses and cardiovascular disease develop in humans. The work was described in two recent publications by University at Buffalo chemical engineers.

Supported by research grants from the National Institutes of Health, the ultimate goal of the project is to define novel strategies to perturb the glycome -- the complete set of an organism's carbohydrate structures in cells -- in ways that lead to the identification of new targets and molecular therapies to combat a broad range of inflammatory diseases.

The binding of white blood cells to blood vessels is a key step in the progression of inflammatory diseases, explained Sriram Neelamegham, Ph.D., UB professor of chemical and biological engineering in the School of Engineering and Applied Sciences, and co-author of both papers. He also is an investigator with UB's New York State Center of Excellence in Bioinformatics and Life Sciences.

"Our goal is to find ways to alter carbohydrate structures or glycans on the surfaces of white blood cells," he said.

But in order to do that, researchers need a far more detailed picture of these structures and the highly complex interactions between glycans, enzymes, genes and proteins, all of which can influence the development of inflammatory disease.

To do this research, Neelamegham's lab uses systems biology, a mathematical and experimental approach that focuses on whole systems of complex biological functions and interactions instead of studying individual units, such as a single gene or protein, in isolation.

"Systems biology is well-suited to this research because it helps us develop the mathematical concepts to enable us to influence and enhance our understanding of how the glycome functions," said Neelamegham. "This then produces clues on how we might manipulate the adhesivity of white blood cells to the blood vessel wall."

Glycans are carbohydrate molecules that mediate the microscopic interactions between white blood cells and blood vessel walls. These interactions play a major role in painful and debilitating inflammatory medical conditions such as asthma, psoriasis, Crohn's disease, reperfusion injury and other cardiovascular ailments.

In a recent paper in The FASEB Journal, the UB researchers describe one of the first studies to take a systems approach to the study of cellular glycosylation, the modification process that is responsible for the attachment of sugar structures to protein and lipid scaffolds. Such biochemical modifications are critical to diverse biological processes, including cell/organ development, immunity and cell adhesion. Abnormal glycosylation also is implicated in diverse diseases, including certain cardiovascular diseases and a cluster of congenital diseases termed Congenital Disorders of Glycosylation.

The paper demonstrates experimental techniques that measure enzyme reaction rates involved in glycosylation, and then draw critical correlations with gene expression, enzyme kinetics and the structures of glycans.

"These techniques enable us to move from genes to proteins and finally to the structures of glycans on cells and individual proteins," said Neelamegham.

The UB paper in Bioinformatics describes a computer model that uses the data produced by those experiments to establish a basis for predicting the structures of glycans on cell surfaces.

"The data produced experimentally allows us to determine key steps in the glycome reaction network that controls the final glycan structure that appears on cells," Neelamegham explained. "This approach then provides an in silico tool that can be applied to perturb the system of interest, such as the glycosylation network."

Those studies, in turn, he continued, can then generate new hypotheses that can be tested experimentally.

"Such an interative approach, using computational and experimental tools, can provide clues as to what reactions must be perturbed in order to alter the carbohydrate structure on cell surfaces in a defined manner," he explained.

The UB researchers noted that their computational and experimental approaches to the problem provide them with a unique insight.

"It's an extremely valuable way to apply engineering principles to biology, it's critical to merge both approaches," said Neelamegham.

In addition to providing new insights for the ultimate development of new drugs and therapeutic strategies, the UB research also is relevant to sectors of the biotech industry, which aim to apply glycan engineering principles during product development.

Source: University at Buffalo