CHAPTER IX: BIOLOGICAL ROLES OR FUNCTIONS OF GLYCANS

So, what are the biological roles or functions of glycans? And, if I were to use one slide to hit home something that we needed the whole organism genetics to get us to, and appreciate, if you had a mutation or if you knocked in genes that were responsible for carbohydrate assembly or carbohydrate synthesis, this picture is worth a thousand words. It's essentially the most dramatic picture of a similar locus, where alternations in the carbohydrate structure, on the protein that displays these polysaccharides, if you will, on cell surfaces, give you very dramatically different phenotype. Obviously, the question is, how do we get to the molecular basis of this, try to really understand what are the fundamental roles in these processes, and to be able to understand the structure function relationship.

So, it gets us to sort of the central molecular picture. And, what I'd like to do is frame these central roles of polysaccharides, using the molecular dogma, if you will, of how DNA makes RNA makes protein. And, we thought that we understood much of life, and genomics was the answer to a lot of the basic questions, which is true in some sense, in terms of understanding pathways. But, if you truly look at it, one of the things that you see with regard to proteins is the fact that the most extensive form of post-translation modification of proteins is glycosilation or the process of attaching carbohydrates to proteins. Because, you're able to get a huge amount of functional diversity.

What do I mean by that? Using erythropointin, which is a biologic, it's a protein that essentially plays a central role in how red blood cells are replenished, you begin to see that one EPO molecule, one protein molecule, has greater than a hundred and fifty unique different carbohydrate structures attached to it. And, that begs the question,

how do these molecules impinge on the functionality of erythropointin, and what are the functional consequences of this, these kinds of attachments?

So, it is fair to say that, as a consequence of our understanding of these carbohydrates attached to proteins, the fact that you are one gene, one protein, and many glycol proteins, the central dogma is truly be revisited in a sense that you're now able to get a huge amount of functional diversity by using a combination of these different carbohydrates that are attached to proteins, so that you can get a diversity on the function.

And, as I walk through some of these examples, you'll begin to see why the roles of these kinds of modification eventually play a role in biological function.

Very simply put, there are two broad families of carbohydrates. One, which are branched, and I'm going to very quickly summarize. The other, which I, earlier, which I summarize in the next slide. And, building on the previous slide, one of the things you begin to see is the fact that glycosilation is the most extensive form of post translation modification that I just mentioned. And, these are determinants of recognition function, protein folding, targeting half life, and stability and specificity.

So, the question is, how do you assemble these? How do you know where they are modified? And, hence, how are they going to affect the functional attributes of a protein? But, in reality, the sites and structures and the abundances of glycans on a given protein have only been established for a handful of glycol proteins. So, you can begin to appreciate that, we're at the early stages of these field, truly trying to understand what the functional consequences of these modifications are, given the fact that we're just beginning to access what the various glycans are on different proteins, such as erythropointin.

If you actually look at the following point, which is you take the top nine of the ten protein-based bio therapeutic products that are used in the clinic, they're glycosilated. They have sugars attached to them, and they have functional consequences in the way these sugar molecules function.

So, part of trying to understand protein function, you truly need to get to access the carbohydrates, and how these carbohydrates are attached to proteins.