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NVVI Van Bekkum thesis award winner 2023 Juan Ernesto Rodriguez Camejo

Glycosylation as a key to improved cancer diagnosis and better immunotherapy effectiveness

Juan Ernesto Rodriguez Camejo studied the role of glycosylation in anti-tumor responses at Amsterdam UMC. His -omics related view on this topic means a leap forward for the glyco-field, as it indicates how glycosylation differences in the tumor micro-environment relate to immunotherapy effectiveness. The knowledge might enable earlier diagnosis and could offer an additional pathway to regulate immune suppression in the battle against cancer. The combined approach this enables is all the more relevant, as a single line of attack doesn't suffice to strike a lethal blow to a tumor.

“About two decades ago, the glyco-field represented a niche in research”, says Rodriguez, a chemist by education. “At the moment studying glycans is still not mainstream, but a range of discoveries has brought it more to the forefront in different fields, including immunology.” His award-winning thesis is actually his second PhD thesis, as in Uruguay he already did a PhD in Chemistry studying glycans in a parasitology setting. Some basics: all cells have a sugar (glycan) coat on their surface. So, in order to recognize a tumor cell, the immune system need to also interact with the sugars in the coating. The process that regulates this is called glycosylation, the modification by which a carbohydrate is covalently attached to a target protein or a lipid.

Playing hard to get

Rodriguez explains: “Of the problems is the complexity of glycosylation, as there are lots of different glycans playing many different roles. For example, DNA/RNA and proteins are made from 4 or 21 building blocks, respectively, that can interact in a particular way. However, in glycosylation there are 'only' 12 different sugar building blocks, but they can interact in multiple ways, leading to more different combinations of these. That makes the pathway difficult to study.”
There are a lot of ways to use high throughput screening on proteins and RNA/DNA, but for glycans this is not directly possible. “That is why glycosylation has been neglected in existing data, for instance from single cell sequencing. You have to figure out the relevant indirect links. That is worthwhile, as these existing big data can still reveal how glycosylation plays a role in cancer. In this case, we cannot directly identify glycans, but we can establish which enzymes that build up glycans are present. These glycans are associated with a myriad of functions and roles that you cannot directly assess.”

Improved diagnosis

To find out more about this, Rodriguez set up a glycosylation related transcriptomic pipeline to explore publicly available data sets for glycosylation in tumor biopsies. The goal: to find glycan-related gene expression signatures associated with clinical outcome of patients. Rodriguez thus found that glycans in pancreatic cancer tissue are different from those in normal tissue and identified signatures associated with more aggressive tumors. These different glycans change how the immune system recognizes tumor cells. In a next step, he identified clear glyco signatures for each cancer type.
“The well-known CA 19-9 tumor marker, discovered long ago, is actually a glycan”, Rodriguez states. “So, glycosylation has been used in the clinic without even realizing it. The newly developed knowledge enables us for the identification of novel tumor markers that could, after a lot of improvement, also be used for earlier diagnosis of pancreatic cancer.”

The knowledge om glycosylation can be used for both diagnosis and treatment. A combined approach for immunotherapy will lead to more effective treatment. An interesting feature of glycans in humans is that they normally end in a particular sugar, named sialic acid, that the immune system recognizes it as 'own'. In general, tumors are covered in an increased amount of sialic acid to trick the immune system. Rodrigez found that sialic acid is increased in pancreatic cancer and showed its role to induce tumor associated macrophage differentiation. A lot of research groups therefore try to target the specific sialic acid in the tumor environment to improve current therapies. “In animal models, results show that targeting sialic acid improved the response to immunotherapy. In our group, we are currently looking into this. Other groups study this approach in relation to breast cancer. Despite that there is still a lot to study, it is clear that it will be helpful to simultaneously target as many suppressive pathways as possible, and sialic acid seems a potential target. In the future we will see more and more of these combined approaches emerge.”

Looking the other way

In his present post-doc research Rodriguez is further zooming in on glycosylation. “For instance, figuring out how different receptors actually carry out their signaling task. Another part of my present work focuses on the role of cells with different receptors for glycans in the tumor microenvironment. For my thesis I concentrated on the tumor side and followed the process inside out. Now I'm looking more at the immune system side and I'm looking outside in, as a way to investigate how glycosylation could be deployed as one of the possible ways to improve immunotherapies. But here is still a lot of work to be done before these improvements might actually be used to the benefit of patients.”

Leendert van der Ent

Juan Ernesto Rodriguez Camejo, 'Unraveling ther tumor glyco-code. Studying the role of glycosylation in cancer progression and immune evasion'. Promotor: Yvette van Kooyk (Who discovered DC-SIGN, a glycan-binding protein (GBP) receptor present on the surface of macrophages and dendritic cells), co-promotor: Juan Garcia Vallejo.