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Glyco-immuno-oncology – Is it Time to Get Excited?

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Glyco-immuno-oncology

Glyco-immuno-oncology is a relatively new discipline which has developed from the fusion of three established and growing fields that are briefly reviewed below [1]. Its foundations lie in the fact that the human proteome is >50% glycosylated [2]. This extra glycan information or 'glyco-code' allows for glycoform dependent intracellular communication between cancer cells and immune cells. This niche field is beginning to reveal translational opportunities that offer great potential benefits.

Immuno-oncology

It has been a slow-burner but the importance of tumor-immune crosstalk is now commonly accepted. The success of immune checkpoint inhibitors in particular has far reaching and profound consequences for how we think about translational research and treatment within oncology; the immune system must now be considered [3]. This new schema has led to translational research focused on previously unthinkable and dangerous concepts, such as promoting angiogenesis and genetic instability, to allow for greater immune infiltration and neo-antigen expression respectively [4,5]. This is truly revolutionary.

Glyco-oncology

It is also commonly accepted that tumors express aberrant, usually truncated glycans, both O and N linked; indeed, these alterations are considered a hallmark of cancer [6]. These changes can occur due to specific mutational events, such as in the case of COSMC [7], but this author, and others, would argue that in the majority of cases aberrant glycosylation is brought about by local micro-environmental stress. It is the only way to explain the relative uniformity of glycophenotype in, for example, breast cancer, against such a backdrop of genetic and transcriptomic diversity.

Mechanistically, these stressors can result in damage to glyco-machinery (include the ER and Golgi), a change in glycosyltransferase (GST) expression levels (often via inflammatory mediators) or simply the overproduction of certain proteins or lack of substrate [8-10]. The impact of these changes for the cancer can be broadly split into intra- and extra-cellular effects: i) Intra-cellular effects, range from driving proliferation to preventing apoptosis, through a variety of direct and indirect mechanisms; ii) Extra-cellular effects range from altering adhesion, altered polarity resulting in proliferation-driving cis-interactions, to immune modulation [10].

Glyco-immunology

It is still to be commonly recognized that glycans are important in immunity, certainly outside of infectious disease, despite nearly one fifth of CD numbers being either lectins or carbohydrates [11]. There are occasional high impact publications, however the field is arguably spread too thinly over too wide a range of pathologies resulting in slightly ad hoc advancement. Although this can be viewed as a weakness, this field is truly multidisciplinary and much can be learnt from this.

For example, it is becoming more and more apparent that there are shared glycan specific mechanisms at play, regardless of the underlying disease and its etiology; this is exemplified by glycan-specific antibodies and lectins that stain both parasites and tumors [12-14]. Needless to say, a comparative analysis of the genomics, transcriptomics and proteomics shows few similarities, however it is through the shared glycans that we can understand how similar immune modulatory mechanisms exist [14]. Similar parallels can be drawn between cancers and other pathogens, changes during pregnancy and chronic inflammatory disease [15-17].

Why bring these three fields together?

These three specific fields should be, and are being, brought together for one main reason: need. As global health improves, and the impact of infectious disease lessens, cancer is becoming an increasing health burden.

When carried on commonly over-expressed proteins, aberrant glycans allow for highly specific targeted therapy

across multiple cancers [18,19]. Beyond this, understanding the processes by which aberrant glycans promote tumor growth and spread opens up a large number of therapeutic opportunities. For example, engagement of siglecs, carried on many immune cells has been seen to allow for tumor progression through a variety of mechanisms [20-23]; these processes are extremely similar to those used by pathogens to evade the immune system [24,25]. Another important example can be found in the galectin field; where galectins potentiate invasion, facilitate immune evasion and allow for increased tumorigenic signaling [26]. Perhaps unsurprisingly, the rewards on offer have driven investment into this field in the forms of glyco-immune checkpoint therapy, and galectin and glycoform targeting therapies [27-29].

The hope, beyond oncology, is that mechanisms uncovered by this need and subsequent cash-injection may help with other seemingly unrelated pathologies with shared glycophenotypes. A good example here is idiopathic pulmonary fibrosis (IPF) and KL-6. KL-6 is an antibody clone which binds to MUC1 carrying sialylated core 1 or core 2 glycans, and is commonly used as a biomarker for IPF and for disease progression [30,31]. Although the role of KL-6 in IPF is not yet well established, the parallels between our work, with MUC1 carrying sialylated core 1 glycans in breast cancer, and others, and IPF pathology can be seen [20,32].

Resources

Beyond capital, to drive this and indeed any field forward requires good tools and resources. **Table 1** summarizes the current tools available to study glycans in both immunology and oncology. Additionally, I would like to take the opportunity to highlight several free online resources that are very useful, especially when approaching this field for the first time.

The CAZy database: Describes the families of structurally related catalytic and carbohydrate-binding modules of enzymes that degrade, modify, or create glycosidic bonds [33].

Functional glycomics gateway: A comprehensive and free online resource provided by the Consortium for Functional Glycomics (CFG) [34].

Glyco-CD: A manually curated repository of CDs which are defined as oligosaccharides or lectins [11].

Glyco-domain viewer: A database of N and O-linked glycan sites found on mammalian proteins [35].

Glyco mine: A predictive method of identifying N, C and O-linked glycans in the human proteome [2].

KEGG glycan database: A collection of experimentally determined glycan structures [36].

Sugar Bind DB: Provides information on known carbohydrate sequences to which pathological organisms specifically adhere [37].

Symbol nomenclature for glycans (SNFG): A universal symbol nomenclature for the graphical representation of glycan structures [38].

UNiCarbKB: An information storage and search platform for glycomics and glycobiological research [39].

Table 1: Current tools available for glyco-immuno-oncological research.

Tool	Pros	Cons
Plant lectins	Cheap and easy to use. Good sensitivity.	Limited specificity. Gives no information regarding scaffold protein.
Recombinant human lectins	Often tagged, these tools are a good starting point for interaction studies.	Expensive
Glycan specific antibodies	Often more specific than lectins.	Often IgM which can cause problems w.r.t. application.
Glyco-form specific glycoprotein antibodies	Very specific owing to need for both glycan and peptide to be present for binding to occur. Often extremely sensitive.	Difficult to develop.
Chemically synthesized glycopeptides	Easy to produce many glycans. Cheap.	Difficulty in producing some sugars, and, by nature short.
Polyacrylamide linked glycans	Long chains of repeated uniform glycans allow for maximal avidity for binding studies.	Biological relevance can be questioned.
Recombinant glycoforms of glycoproteins	The most biologically relevant tool for studying glycoform specific responses to specific glycoproteins.	Expensive and time-consuming to produce. Difficulties in producing glycoproteins with complex glycans.
Mass Spectrometry	Unparalleled sensitivity and specificity for glycan determination and quantification.	Difficult to use for high throughput studies – although becoming increasingly possible. Expensive and time consuming.
Transfected, transduced, mutated or engineered cell lines, including GlycoDisplay and glycocalyx editing	Biologically relevant and, for simple glycans, extremely robust.	There are often technical and biological problems when expressing complex glycans.

The Future

In recognition of the weight of evidence that supports the importance of glycans in cancer development, especially in the light of the impact on the immune compartment, the need for glyco-phenotyping is being voiced strongly [29]. By using lectin and transcriptomic approaches, and possibly high throughput mass spectrometry of specific 'signpost' glycopeptides, it would be possible to develop a new method of categorizing tumors [40,41]. If certain signatures were associated with specific form of glyco-immune modulation then appropriate glycan or glycoform-specific therapies would be given. This may, in some quarters be seen slightly regressive, as we are moving into DNA and RNA dominated personalized medicine, but it is logical.

Therapies are being developed even without such a paradigm shift; there are several groups, and increasing number of biotechs, working on inhibiting glycan-immune modulation and targeting specific glycoforms of commonly expressed and disease-relevant glycoproteins [29,42]. It is a sensible move in a crowded therapeutic marketplace; however translation of this biology is likely to be difficult. Many of these mechanisms are known, or believed, to be vital for immune homeostasis, therefore drug-induced systemic dysregulation has the potential to invoke profound side-effects. Further to this it should not be forgotten that these glycoforms, and their effects, have a healthy physiological role – so although targeting the glycan and the protein achieves much greater specificity and sensitivity than the protein alone, we cannot become complacent and assume absolute specificity.

At this point, it is additionally important to draw your attention to two potential issues that need to be addressed in the near future. Firstly, the majority of recombinant proteins for clinical and research use are manufactured in Chinese hamster ovary (CHO) cells (K1 clone) – these are cells that cannot O-glycosylated beyond sialylated core 1 [43]. Clearly these therapies work, however, could they be better if expressed in systems that carry the glyco-machinery for a different glycophenotype? Are there therapies that never made it to the clinic because although the protein was correct, their glycans inhibited their functionality?

Secondly, the impact of glycans on antibody-epitope recognition has not been fully explored; data using antibodies that shows quantitative or even qualitative differences may simply be a result of a glycan change within the target epitope. Our group has seen glycan dependant differential binding curves, in recognition of the antigenic PDTR epitope within the MUC1 tandem repeat, since the 1980s [44]. This is not new, it is just niche; we all need to be aware that any epitope which contains a serine, threonine or an appropriately flanked asparagine (Asn-X-Ser, Asn-X-Thr or Asn-X-Cys) should be considered 'changeable' by glycan alterations.

Although both of the above examples are slightly alarming, they are surmountable, and they are beginning to be addressed. Indeed, we are seeing the emergence of a new class of glycoform specific antibodies and chimeric antigen receptors for potential therapeutic use, and glycoengineering of CHO cells to address specific needs [19,28,45,46].

Conclusion

With improving resources and growing interest and investment, the future looks bright for this field. Glycobiology in the context of immunology and oncology should not be ignored, and instead be championed and understood. There are many, many more discoveries to be made as we begin to unpick this fascinating, and occasionally frustrating, ultimate level of biological information.

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Competing Interests

The author has no competing interests.

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