Perspective: small molecules as players in targeted therapies

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Abstract

In this insight report, author discusses the prospect offered by small molecules for the development of targeted therapies. The author also talks about monoclonal antibodies and antibody recognition in human body and why carbohydrate antigen targeting appears to be a promising playground in near future.

Introduction

As the Centers for Disease Control and Prevention points out, breast cancer in USA, and Not counting some kinds of skin cancer, is the most common cancer in women, irrespective of race or ethnicity. The second most common cause of death from cancer among white, black, Asian/Pacific Islander, and American Indian/Alaska Native women. Still in 2015, 224147 women and 2,125 men in the United States were diagnosed with breast cancer and 41,150 women and 405 men in the United States died from breast cancer. The only way to prevent and cure cancer is through innovative research.
The way our group thought of doing it is by designing small molecules as in targeted therapies. The concept and the technique, nowadays, is highly endorsed by the American Association for Cancer Research and is a radical improvement over traditional.

Targeted therapies or rational drug design is normally based on the knowledge of the three-dimensional spatial arrangement of the protein molecular complex and structural analyses of receptors/targets provide us with an effective tool for the development of disease therapeutics. The general notion about targeted therapies are that they are expected to be more effective than current treatments and do not so much impact normal cells. Several therapies based on mechanisms that target critical checkpoints in signaling pathways, progression from normal to tumorigenic cells are gaining more traction. In the last couple of decades, the US Food and Drug Administration (FDA) has approved more than a dozen monoclonal antibodies (mAbs) to treat certain types of cancers. Clinical trials of newer mAbs are now being done on many types of cancer. While many pharma giants compete with each other for their first-in-line immunotherapeutic products, patient safety and health should be monitored for a longer term to determine how each of these drugs fare in progressing survival rates over conventional methods like chemotherapy.

Nevertheless, mAb based immunotherapy together with molecular innovation and potent target discovery are here to stay for the next generation of diagnostics and personalized medicine. In my previous life as a structural bioinformatician, I was investigating antibodies reactive to tumor-associated carbohydrate antigens that play a major role in many metastatic cancers. Neo-carbohydrate antigens are chemical aberrations found on the cell surface of many tumors like breast, lung, prostate etc. Our findings change the older notion about antibody recognition in our body. Antibodies reactive against these neo antigens follow a different developmental pathway. They mostly proceed via the Thymus cell independent pathway in contrast to the what we find in immunology textbooks. For antibodies against Thymus cell-dependent antigens, the acquisition of high reactivity to antigens is known to proceed via antigen driven evolution based on somatic hypermutation (mutational changes in the somatic cells of our body)\(^1\).

We have shown here that mother antibody cells or the germline Lewis Y Reactive B cells yield higher affinity clones as a result of a somatic diversification. The B cells or the B lymphocytes are responsible for antigenic recognition. The germline antibody (precursor antibody) is preformed to recognize salient structural fragments of the carbohydrate antigens. Accumulating discrete mutations in their structure as part of diversification has only recently been addressed. This mutational process yields high probability clones that accommodate better fine structures of the antigen fragments. This reflects a strategy different from the classical theory of antibody maturation. This study highlighted the occurrence of thymus independent antibody related to a single precursor family which is a first of its kind. Thus, as our knowledge about the structural details of antibody-antigen interaction broadens, we may be able to design better antibodies, as well as design improved antibody based vaccines through more refined reverse-engineering concepts based on the knowledge of antibody structural plasticity and specificity, paving the path towards improved immunotherapy for cancer patients.

As an obvious next step towards developing a small molecule therapeutics, I was involved in the development of a peptide referred to as p109/P6 that functions as an antigenic mimic of the Lewis Y (carbohydrate antigen) as p109/P6 binds to an anti-Lewis Y antibody. Molecular modeling indicates that the peptide sequence should contain certain amino acid types like Arginine, Tyrosine, Tryptophan, and Serine that are found to interact with saccharide units. I have exploited these structural rules to predict the kinds of structural conformation these peptides will adopt as carbohydrate mimics. This is a key concept utilized to design immunogenic agents to induce anti-carbohydrate cross reactive response that can overcome the problem of low titer values when carbohydrate antibodies bind to these pathogens. The peptide clearly combines the advantages of antibodies and small molecules that induce inhibition of cell adhesion and cell aggregation\(^2\) presumably through interactions with cellular receptors, at the
same time being proapoptotic in nature when targeted against carbohydrate antigens\(^3\). The unique advantage in targeting carbohydrate antigens by mimetic peptides is that multiple proteins and lipids on cancer cells can simultaneously be modified with a singular carbohydrate structure. Thus, targeting carbohydrate antigens broadens the spectrum of antigens recognized by the immune system.

References

