INSIGHTS FROM OUR EXPERTS

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DISCUSSING MHC PEPTIDE ANALYSIS WITH EUSTACHE PARAMITHIOTIS

We recently sat down with our Vice-President of Research and Development, Eustache Paramithiotis to discuss some of the finer points of MHC peptide analysis, why it is important for a complete understanding of an immune response, and how it is supporting new waves in drug development.

Q: Let's begin with the basics, what is the MHC system and how does it help regulate immune responses?

A: The immune system surveys what is going on in the body through the MHC. There are three kinds of MHC, Class I, Class II, and non-classical, all presenting peptides and sometimes other things like lipids. This is how T cells do their surveillance and identify anything unusual or "non-self". Thus, the MHC is essential for launching an immune response, the first step of it all!

Q: With the recent advancement of immune therapies, is MHC peptide presentation critical information to know?

A: In fact, it is absolutely essential! Modern immune therapies involve the host immune system. The antigen is either directly provided to educate the immune cells, or modified cells, as per CAR-T cell therapy, are introduced to attack the tumor. Some immune responses are obtainable with non-MHC based system, including innate immunity and NK cells, but an optimal and complete immune response will require MHC presentation.

Q: Characterizing MHC peptides is a significant technical challenge, how does your team tackle it?

A: Immunologists had determined many years ago that antigen was presented in the 'context of MHC', a concept developed from functional studies, though they didn't know how that actually worked. The concept was confirmed by crystal structures, which showed directly that antigen – in this case a peptide – was embedded in the MHC and the MHC-peptide complex was what the T cell receptors bound to.

The peptide's length and composition may vary with the type of MHC, but the concept remains the same, a peptide embedded in a macromolecule and both presented together. All the analytical techniques that have been developed over time to isolate, process, and analyze peptides come into play here. Having the capability to perform accurate and reproducible mass spectrometry and evaluate results with strong bioinformatic tools is essential for productive experiments. All of which we invested in and can now do at scale.

Q: Can you expand on the importance of the direct measurement of peptides?

A: The most physiologically relevant way to see what the host is presenting is to look directly in the tissue. Given the structure of the MHC Class I or Class II, presented peptides tend to have themes in their sequence, anchor points and motifs, which led to the use of computer algorithms to predict what would be presented. With all the projects we have done, we have seen that what is actually presented is far more complex than what the algorithms are able to tell us. The algorithms are much better at modelling peptide-receptor interactions once you have a peptide sequence, but since we don't fully understand the regulation of antigen processing and selection for what will get loaded onto the MHC it is difficult to accurately predict what will get presented.

A: So, when it comes to the kind of personalized targets that are ideal for cancer immunotherapies, including neoepitopes (peptides with somatic mutations), prediction is inefficient. The variety of modifications we can observe directly in tissues is much broader than the one obtained with prediction algorithms. Nowadays, if you cannot directly observe what is being presented, there will be gaps in your understanding.

Q: In addition to direct detection, what are some of the learnings about MHC peptides that differentiates Caprion-HistoGeneX's approach from what others are doing?

A: MHC presentation is necessary to initiate and maintain an immune response, but it's not the only thing you need. To be able to judge how well peptides induce an immune response, you need a range of immune monitoring or immune evaluation capabilities. That is where Caprion-HistoGeneX comes in and has put all those pieces together. We provide the complete picture of all the factors involved, from identifying the target in tissue, to the levels of MHC I expression, and to characterizing the responsiveness of the host T cells to target.

Q: How does the Antigen Atlas fit into this picture and your ability to characterize the MHC presentome?

A: The Antigen Atlas is primarily a prioritization tool. It was built to help prioritize the targets based on their lack of presentation in other tissues. The Atlas contains MHC I presented peptides from a library of healthy and tumor adjacent tissues (usually a bit more inflamed than healthy tissue), and it includes a wide range of different MHC I alleles. The database has on the order of 400,000 entries right now and is often updated to stay current.

If you have a peptide you are interested in from a target tissue, you can check if it is presented in other tissues. Typically, therapies are concerned with understanding on-target and off-target effects. Immune therapies as well, but also need to understand on-target but off-tissue effects, because you don't want to trigger an attack to the liver 5 years after curing a lung cancer. A large database, made to our quality standards, can also do a lot of other things than just help prioritize targets. For example, you can use it to better understand baseline mutation presentation in healthy tissues, identify protein presentation hotspots that are independent of the MHC I alleles an individual expresses, and identify tissue-specific presentation patterns to name a few.

Q: In the next few years, what innovations do you think MHC peptide analysis will help drive?

A: Right now, all of it is focused on MHC Class I and effector/cytotoxic T cells, because that is the pointy end of the stick. To mount a complete robust immune response with memory, you need Class II involvement and that has not yet become as prominent in the current analysis. We will eventually need to know what helper and regulatory T cells as well as B cell are presenting, which means both Class I and Class II MHC.

Another aspect we will need to further investigate is the heterogeneity of presentation. Right now, we don't really know where in the tissue peptides are presented. Are they presented in a homogenous way, or are they presented in pockets, which may be less accessible to infiltrating lymphocytes? A better understanding of peptide distribution, especially when it comes to solid tumor therapies, is going to become very important.

Q: What are your key takeaways or what you would like the readers to know about MHC peptide analysis with Caprion-HistoGeneX?

A: Key takeaways would be that MHC peptide analysis is now practical, it's doable on just about any kind of system. It is also necessary for the understanding of immune responses. And finally, it should be considered as an essential part of a larger assessment of immune function. Caprion-HistoGeneX can evaluate, understand, and monitor the entire immune response. You get to find the antigens and what is presented, but then we'll also help you figure out what to do with them and how to get them to react.

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