Editorial

Is there a value for definition of human leukocyte antigen-associated peptidomes?

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Comment on: Abelin JG, Keskin DB, Sarkizova S, *et al.* Mass Spectrometry Profiling of HLA Associated Peptidomes in Mono-allelic Cells Enables More Accurate Epitope Prediction. Immunity 2017;46:315-26.

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In the article, *Mass Spectrometry Profiling of HLA-Associated Peptidomes in Mono-allelic Cells Enables More Accurate Epitope Prediction* by Abelin *et al.* (1) which was published in the February 2017 issue of Immunity the authors present a novel methodological approach to define peptidomes presented on major histocompatibility complex (MHC) class I alleles. The MHC of man is called human leukocyte antigen (HLA), of mice, H2, and of rats, RT1, to name a few examples of names of the MHC of different species that are relevant for biomedical research.

The possibility to define peptides presented on MHC class I molecules was developed by Rammensee and co-workers (2). Olaf Rötzschke and Kirsten Falk discovered that peptides could be eluted from MHC class I molecules by strong acid treatment. Subsequent assessment of the eluted peptide pools by mass spectrometry and sequencing lead to the identification of allele-specific binding motifs of MHC class I molecules. Sette and Strominger pioneered the elution of peptides from MHC class II molecules and identified the first ligands and ligand binding motifs of MHC class II molecules (3, 4). Technological progress by liquid chromatography-tandem mass spectrometry (LC-MS/MS) enabled detection and sequencing of individual eluted ligands. The observed information has led to the elucidation of MHC class I and II ligand binding motifs for various MHC alleles (5, 6) and various species. It became apparent that there is a great variety in the binding requirements of peptide ligands between different MHC class I and II alleles. Subsequently, researchers assessed the variability of T cell recognition of eluted ligands and used this information to assess aspects of tumour immunity (7), transplant rejection, infection (8) and autoimmunity (9-12).

In the beginning of this work, researchers used large quantities of tumour or spleen cells to purify MHC class I and II molecules and subsequently, to elute peptides (13, 14). Also, EBV-transformed B cell lines were used. Since such cells express various MHC class I and II alleles it depended much on the specificity of the MHC binding antibody used for purification of individual MHC allelic variant molecules to discover allele-specific binding peptides. Nevertheless, by this multi-allele approaches, interference of different peptide binding alleles based on processing or other pre-existing conditions could not be excluded. In the study by Abelin *et al.* (1) the authors used a novel approach for accurate definition of MHC bound peptides of different MHC class I alleles. In contrast to earlier studies, they used mono-allelic B cells generated by transduction of B721.221 cells with a retroviral vector. This retroviral vector coded for a single MHC class I allele. The authors determined MHC class I bound peptides from 16 MHC class I alleles. In contrast to a multi-allele approach, this novel single-allele approach has the advantage to be able to unambiguously assign peptides to MHC class I alleles and therefore based on this to create new predictors of binding algorithms of peptides to bind to specific MHC class I alleles. Also, the number of cells that is needed for this type

of approach is 10× lower as compared to the multi-allele approach. The authors also determined mRNA transcripts from four different B721.221 cells each expressing a distinct MHC class I allele. Using extensive database search strategies, firstly they defined the relationship of expression and affinity of peptides as well as the impact on processing pathways. Subsequently, neural-network classifiers were trained with a multistep approach. This resulted in better predictions of peptides binding to certain MHC class I alleles. The analyses also gave more insight into antigen processing and presentation rules. Altogether 24,000 MHC class I bound peptides were identified.

Why is it of relevance to do this type of work? MHC class I and II molecules present peptides to T cells. Therefore, only peptides that are presented on MHC molecules can activate T cells through the T cell receptor (TCR). The knowledge regarding specific peptides that potentially raise certain immune responses is of great relevance. For example, this knowledge can be used for definition of tumour vaccines (15, 16). Also in autoimmune diseases like multiple sclerosis, the knowledge regarding specific sets of presented peptides in the target organs of the autoimmune responses is of relevance (9, 11). This knowledge can potentially be used for definition of peptides that can be used for tolerance approaches.

Everyone expresses a defined set of MHC class I and II alleles. Since the MHC class I and II alleles are extremely polymorphic, also the peptide sets that are presented on MHC class I and II molecules differ between individuals grossly. Presently novel technology is introduced to define the variations in HLA haplotypes in greater detail (17). The number of allelic variants of known MHC class I and II alleles is further increasing (18). To do selective immunological interventions, the exact processing, presentation and specifically binding requirement of peptides to targeted MHC alleles used for interventions in the treated individual need to be known. The approach of Abelin *et al.* (1) is an improved way to define biochemical binding characteristics for different MHC class I alleles. Also, others have used advanced technology to assess MHC-associated immunopeptidomes (19). Possibly this knowledge can help on the long run to enable improved peptide based therapeutic interventions for the treatment of tumours, transplant rejection, infection or autoimmunity and could also be of relevance for diagnostic reasons. Such an improved approach with analyses of monoallelic MHC class II expressing B cells to define MHC bound peptides has not been performed for MHC class II alleles so far. Much efforts are presently performed with dendritic cells (DC) to elute peptides from MHC class II molecules (20, 21). Also for MHC class II molecules improved prediction algorithms would be of relevance to use this knowledge for immunological interventions to a larger and possibly more successful extent. Therefore, much more efforts are necessary to define the relevant portion of the complete human MHC class I and II bound peptidomes and of peptidomes associated with certain disease conditions.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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