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MHCing the tumour's dark genome

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Immune recognition of tumours is primarily thought to be driven by the presentation of tumour neoantigens – peptides derived from nonsynonymous mutations in protein-coding regions – on MHC class I molecules, which are often specific ('private') to an individual tumour. By contrast, other types of antigen, such as cancer germline antigens (CGAs) and melanoma-associated antigens, are shared across tumours and therefore have been leveraged as vaccine targets. However, the potential repertoire of MHC class I-bound peptides extends beyond the 2% of the genome that is known to code for functional proteins; translated products of cryptic open-reading frames, namely introns, non-coding RNA, untranslated regions (UTRs), off-frame sequences and intergenic regions, can also be presented on MHC molecules.

In this preprint (not peer-reviewed), Lozano-Rabella et al. show that this cryptic class of MHC class I-binding peptides is much more abundant in tumours than are neoantigens or tumour-associated antigens. Using a proteogenomics approach, they identified 517 unique, non-canonical tumour ligands (nonC-TLs) from nine tumour cell lines, mainly derived from 5′ UTRs and off-frame transcripts, some of which were found in up to five of the tumours. They detected naive T cells specific for three of the candidate nonC-TLs – 5′U-HOXC13, 5′U-ZKSCAN1 and non-coding C5orf22C – that, once expanded, could recognize multiple other tumour cell lines, thus identifying these antigens as attractive vaccine targets. Importantly, they found that although pre-existing T cell responses to nonC-TLs were not detected, thereby implying that these ligands are not involved in tumour immune surveillance, the nonC-TLs are highly immunogenic and specific to tumour cells, with little to no T cell response to healthy cells observed in their assays. However, owing to the limitations of mass spectrometry as used in this study, and other studies that have suggested that the nonC-TLs are expressed in healthy tissue, this lack of T cell response should be interpreted with caution.

This study highlights an underappreciated class of tumour antigens as an immunogenic and promising shared therapeutic target. With a larger and more diverse sample set, the novel and comprehensive mass-spectrometry and computational pipeline used here has the potential to identify additional nonC-TL antigens that are widely immunogenic and expressed on HLA alleles other than HLA-A*11:01 and HLA-A*03:01, which are the most commonly presenting alleles in their dataset. Evaluation of the expression of nonC-TLs in a broader set of healthy tissues could be used to indirectly assess for potential toxicities, which have been observed in clinical trials using CGA-specific engineered T cells, and to

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validate that these cryptic antigens are indeed specific to tumour cells. Furthermore, it would be interesting to investigate the biological reasoning for the shared expression of these nonC-TLs between patients, as their non-functional role in the cell suggests that they would not contribute to tumour fitness. It will also be important to assess if these cryptic antigens are sufficiently immunogenic to induce a robust immune response after vaccination.

References

Lozano-Rabella M. et al. Immunogenicity of non-canonical HLA-I tumor ligands identified through proteogenomics. Preprint at bioRxiv 10.1101/2022.11.07.514886 (2022)

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