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AUTHOR'S VIEWS

Cancer neoantigens and immunogenicity: mutation position matters

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ABSTRACT

Cancer mutations can elicit protective immunity. Computational methods are critical for selecting these neoantigens for immunotherapy. While significant progress has been made in the field in predicting peptide presentation, our understanding of which mutated peptide is recognized as foreign by T cells remains limited. We used mouse vaccination studies to examine the features of immunogenic neoantigens and demonstrated that the mutation position is an important criterion for predicting neoantigens.

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Developing tumors accumulate mutations that can give rise to abnormal proteins or peptides. These mutated proteins may be processed into short mutant peptides that are displayed by molecular histocompatibility complex class I (MHCI) molecules on the surface of tumor cells. If recognized as foreign by CD8 T cells, these mutated peptides called "neoantigens" stimulate CD8 T cells to kill tumor cells. Many pre-clinical and clinical studies have shown that neoantigen-targeted immunotherapy can generate an anti-tumor response.[1] These findings have paved the way for the development of novel strategies that specifically exploit neoantigens. However, only a small fraction of neoantigens appear to elicit a T cell response. Indeed, elicitation of immunogenicity is a multistep and complex process including: (1) generation of mutated peptides by the proteasome, (2) peptide translocation to the endoplasmic reticulum and loading onto MHCI, (3) transport of the stable peptide/MHCI complex to the surface for presentation to CD8 T cells, (4) recognition of the mutant peptide as foreign by T cells.[2] Neoantigen-targeted immunotherapy relies on prediction algorithms to select candidates likely to induce an anti-tumor T cell response in patients. While substantial progress has been made in methods that can predict peptide binding and presentation by MHCI using immunopeptidomics data, prediction of the final step, e.g. recognition of mutant peptides by T cells, remains fairly immature.

In our study, we chose to directly look at neoantigen-specific T cell responses by screening a large set of mutant peptides from preclinical tumor models. We identified expressed peptides containing single amino acid mutations from four different mouse tumor cell lines by whole-exome sequencing and RNA sequencing analysis. We next selected neoantigen candidates based on predicted MHCI binding affinity. We then screened more than 400 total mutant peptides for immunogenicity by vaccinating healthy mice and found that ~10% of them induced a CD8 T cell response as measured by interferon (IFN) gamma ELISpot.

It is generally admitted that immunogenic epitopes inducing a CD8 T cell response tend to have higher binding affinity. Interestingly, recent studies on cancer neoantigens suggest that the relative affinity to MHCI of the mutant peptide, when compared with the affinity of the wild-type (wt) counterpart, is a better predictor of T cell response.[3–6] We hypothesized that the contribution of these two predictors of immunogenicity is dependent on the mutation position: mutations at anchor residues and mutations at non-anchor residues.

We determined that for mutations at a non-anchor position, the binding affinity of the mutant peptide for MHCI molecule (absolute affinity) is a strong predictor of immunogenicity. In addition, we found that the majority of mutations tend to be centrally located in the peptides of this subgroup, and therefore likely in contact with the T cell receptor (TCR) as previously proposed.[7] Thus, CD8 T cells likely differentiate between "foreign" and "self" antigens when the non-anchor mutation is seen by the TCR.

On the contrary, when the mutation is at an anchor position, the relative affinity between the mutant and the wt counterpart peptide strongly associates with T cell activation while the absolute affinity is not a clear predictor of immunogenicity. In this case, the wt counterpart epitope is likely not or poorly presented to T cells and the anchor mutation creates a novel epitope that has never been seen by the immune system, and therefore is recognized as "foreign" by CD8 T cells. We validated our findings using human antigens from publicly available datasets.

We also looked at other biophysical properties that have previously been suggested to predict immunogenicity, e.g. stability, microbial similarity, physicochemical properties of TCR contact residues,…[3,4,8,9] and these properties did not seem critical in predicting immunogenicity for both mouse and human datasets in our study.

Finally, we developed a positional model and showed that the prediction of immunogenicity can be improved when the position of the mutation (e.g. anchor or non-anchor) is considered.

In conclusion, our study highlights that the generation of large-scale data in pre-clinical models helps improve

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algorithms to predict immunogenicity and is translatable to the human immune system. With advances in sequencing technologies and new emerging strategies focusing on TCR recognition, new insights in TCR specificity should emerge and thus help further improve the accuracy of algorithms predicting T cell recognition and neoantigen immunogenicity.

Disclosure of potential conflicts of interest

All authors are employees of Genentech.

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References

1. Yarchoan M, Johnson BA, Lutz ER, Laheru DA, Jaffee EM. Erratum: targeting neoantigens to augment antitumour immunity. Nat Rev Cancer. 2017;17(9):569. doi:10.1038/nrc.2017.74.
2. Capietto A-H, Jhunjhunwala S, Delamarre L. Characterizing neoantigens for personalized cancer immunotherapy. Curr Opin Immunol. 2017;46:58–65. doi:10.1016/j.coi.2017.04.007.
3. Balachandran VP, Łuksza M, Zhao JN, Makarov V, Moral JA, Remark R, Herbst B, Askan G, Bhanot U, Senbabaoglu Y, et al. Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer. Nature. 2017;551(7681):512–516. doi:10.1038/nature24462.
4. Duan F, Duitama J, Al Seesi S, Ayres CM, Corcelli SA, Pawashe AP, Blanchard T, McMahon D, Sidney J, Sette A, et al. Genomic and bioinformatic profiling of mutational neoepitopes reveals new rules to predict anticancer immunogenicity. J Exp Med. 2014;211(11):2231–2248. doi:10.1084/jem.20141308.
5. Ghorani E, Rosenthal R, McGranahan N, Reading JL, Lynch M, Peggs KS, Swanton C, Quezada SA. Differential binding affinity of mutated peptides for MHC class I is a predictor of survival in advanced lung cancer and melanoma. Ann Oncol. 2018;29(1):271–279. doi:10.1093/annonc/mdx687.
6. Rech AJ, et al. Tumor immunity and survival as a function of alternative neopeptides in human cancer. Cancer Immunol Res; 2018 Mar;6(3):276–287. doi:10.1158/2326-6066.CIR-17-0559. Epub 2018 Jan 16.
7. Yadav M, Jhunjhunwala S, Phung QT, Lupardus P, Tanguay J, Bumbaca S, Franci C, Cheung TK, Fritsche J, Weinschenk T, et al. Predicting immunogenic tumour mutations by combining mass spectrometry and exome sequencing. Nature. 2014;515(7528):572–576. doi:10.1038/nature14001.
8. Calis JJ, Maybeno M, Greenbaum JA, Weiskopf D, De Silva AD, Sette A, Keşmir C, Peters B. Properties of MHC class I presented peptides that enhance immunogenicity. PLoS Comput Biol. 2013;9(10):e1003266. doi:10.1371/journal.pcbi.1003266.
9. Chowell D, Krishna S, Becker PD, Cocita C, Shu J, Tan X, Greenberg PD, Klavinskis LS, Blattman JN, Anderson KS. TCR contact residue hydrophobicity is a hallmark of immunogenic CD8+ T cell epitopes. Proc Natl Acad Sci USA. 2015;112(14):E1754–62. doi:10.1073/pnas.1500973112.