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Abstracts BOOK

CANCER RESEARCH INSTITUTE

CIMT Cancer Immunotherapy

eati.

AACR American Association for Cancer Research

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Keywords : ribosome profiling, neoantigen, Ribo-seq.

References :
Ji, Z., Song, R., Regev, A., and Struhl, K. (2015). Many lncRNAs, 5'UTRs, and pseudogenes are translated and some are likely to express functional proteins. eLife 4. Keskin, D.B., et al. (2019). Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial. Nature 565, 234-239. Ott, P.A., et al. (2017). An immunogenic personal neoantigen vaccine for patients with melanoma. Nature 547, 217–221. Erhard, F., et al. (2018). Improved Ribo-seq enables identification of cryptic translation events. Nat Methods 15 :363-366.

B169 / Neoantigen prediction for cancer vaccine across entities

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Different strategies of cancer immunotherapy have shown outstanding success in a number of patients across various tumor types. Cancer genome-based identification of patient-specific neoantigens plays an important role in cancer immunotherapy, e.g. vaccine strategies. The expression of neoantigens by tumor cells allows the immune system to distinguish cancer cells from normal cells and, potentially leads to activation of the patient's own immune effector cells to specifically eradicate tumor cells. However, only a small fraction of genomic mutations may lead to immunogenic neoantigens and thus a reliable prediction of immunogenic neoantigens is required. We developed a pipeline to determine the patient´s HLA type and to predict MHC class I and II neoantigens based on the analysis of the next-generation sequencing data. Our pipeline is able to predict neoantigens from nonsynonymous mutations, small insertions/deletions and gene fusions, and has already been successfully applied to predict neoepitopes in various cancer patients. Among 24 vaccinated neopeptides, more than 80% can either expand pre-existing T-cell responses or induce new T-cell specificities after vaccination in cancer patients (n=4) across tumor entities. Importantly, we demonstrate that neopeptides arising from fusion genes can also induce T-cell responses. Currently, this pipeline is being optimized and further experimental validation is conducted to identify which fusion-derived neoepitopes among the vaccinated neopeptides can stimulate T cell responses. Perceptively, we aim to efficiently translate the neoantigen-based strategy to clinical application, e.g. TCR-specific engineered T-cell therapy.

Keywords : Neoantigen, Fusion, Immunotherapy, Cancer vaccine.

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Ko²alo²lu, Z., Zörnig, I., Halama, N., Kaiser, I., Buchhalter, I., Grabe, N.... & Jäger, D. (2016). Identification of immunotherapeutic targets by genomic profiling of rectal NET metastases. Oncoimmunology, 5(11), e1213931.

B170 / HLA ligandome analysis reveals an antigen processing signature required for HLA class I presentation and CD8+ T cell responses

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CD8+ T cells recognize peptides displayed by HLA class I molecules, discriminating cancer cells. Difficulty in predicting HLA class I ligands is attributed to the complexity of the antigen processing pathway across the cytosol and the endoplasmic reticulum (ER). Here, we captured natural HLA class I ligands displayed by multiple types of cancer cell lines using HLA ligandome analysis that employs mass spectrometry, and analyzed the imprints of antigen processing. The comprehensive analysis of source-protein sequences flanking the ligands revealed that the frequency of proline at amino acid positions 1-3 upstream of the ligands was selectively decreased. The depleted proline signature was the strongest among all the upstream and downstream profiles. Experiments using live cells demonstrated that the presence of proline at upstream positions 1-3 attenuated CD8+ T cell responses against a model cancer antigen. Other experiments in which N-terminally flanking antigen precursors were confined in the ER demonstrated an inability to remove upstream prolines regardless of their positions, suggesting a need for synergistic action across cellular compartments for making the proline signature. Our results highlight an antigen processing signature that could affect HLA class I peptide repertoire formation and CD8+ T cell responses.

Keywords : Tumor antigens.

References :
J Immunol. 2019 May 15;202(10):2849-2855. doi : 10.4049/jimmunol.1900029.

B171 / Immunogenicity of HLA class II-restricted neoantigens derived from driver mutations

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Recently, increasing attention has been paid to neoantigens that are derived from somatic genetic mutations specifically present in cancer cells. Since they can be recognized as non-self by the immune system, they are expected to induce stronger immune responses than non-mutated self-antigens. In particular, since "driver mutations" that are directly involved in malignant processes are frequently shared by patients with various types of cancers and do not disappear easily by immune escape, they could represent appropriate off-the-shelf targets for cancer immunotherapy.

In the current study, we evaluated the immunogenicity of 10 well-known driver mutations, including KRAS-G12D, KRAS-G12V, KRAS-G12C, KRAS-G12R, KRAS-G13D, NRAS-Q61K, NRAS-Q61R, PIK3CA-E545K, PIK3CA-H1047R, and C-Kit-D816V, which are frequently expressed in various cancers using peripheral blood mononuclear cells from healthy donors (n = 25). Of the 10 synthetic peptides (27 mer) derived from these mutations, the six peptides from KRAS-G12D, KRAS-G12R, KRAS-G13D, NRAS-Q61R, PIK3CA-H1047R, and C-Kit-D816V induced T cell responses. In particular, more than 10% of the donors showed immune responses to PIK3CA-H1047R, C-Kit-D816V, KRAS-G13D, and NRAS-Q61R. All six peptides induced HLA class II-restricted CD4+ T cell responses ; notably, PIK3CA-H1047R contained at least two different CD4+ T cell epitopes restricted to different HLA class II alleles. In addition, PIK3CA-H1047R and C-Kit-D816V induced antigen-specific CD8+ T cells as well, indicating that they might contain both HLA class I- and class II-restricted epitopes.

Our findings suggested that frequent driver mutations are not always less immunogenic, since six of 10 well-known driver mutations induced specific T cell responses. Since the identified neoantigens might be shared by patients with various types of cancers, they have the potential to be promising off-the-shelf cancer immunotherapy targets in patients with the corresponding mutations.

Keywords : neoantigen, driver mutation, HLA class II.

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Iizumi S, Ohtake J, Murakami N, Kouro T, Kawahara M, Isoda F, Hamana H, Kishi H, Nakamura N, Sasada T. Identification of Novel HLA Class II-Restricted Neoantigens Derived from Driver Mutations. Cancers (Basel). 2019 Feb 24 ;11(2). pii : E266. doi : 10.3390/cancers11020266.