Membrane-Localized Mutations as Predictors of Checkpoint Blockade Efficacy in Cancer

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Abstract : Tumor cells have mutations resulting from genetic instability that the immune system can actively recognize. Immune checkpoint immunotherapy (ICI) is commonly used in the clinic to re-activate immune reactions against mutated proteins, called neoantigens, resulting in tumor remission in cancer patients. However, only around 20% of patients show durable response to ICI. While tumor mutational burden (TMB) has been approved by the Food and Drug Administration (FDA) as a criterion for ICI therapy, the relevance of the subcellular localizations of the mutated proteins within the tumor cell has not been investigated. Here, we hypothesized that localization of mutations impacts the effect of immune responsiveness to ICI. We analyzed publicly available tumor mutation sequencing data of ICI treated patients from 3 independent datasets. We extracted the subcellular localization from the UniProtKB/Swiss-Prot database and quantified the proportion of membrane, cytoplasmic, nuclear, or secreted mutations per patient. We analyzed this information in relation to response to ICI treatment and overall survival of patients showing with 1722 ICI-treated patients that high mutational burden localized at the membrane (mTMB), correlate with ICI responsiveness, and improved overall survival in multiple cancer types. We anticipate that our results will ameliorate predictability of cancer patient response to ICI with potential implications in clinical guidelines to tailor ICI treatment. This would not only increase patient survival for those receiving ICI, but also patients' quality of life by reducing the number of patients enduring non-effective ICI treatments.

Keywords : cancer, immunotherapy, membrane neoantigens, efficacy prediction, biomarkers
Conference Title : ICATCTI 2022 : International Conference on Advanced Technology in Cancer and Tumor Immunology
Conference Location : New York, United States
Conference Dates : October 06-07, 2022