

A Novel Approach for Guiding Immunotherapies Toward Treating “Cold” Tumor Cells

Method developed by Children’s Hospital of Philadelphia researchers has helped identify target proteins linked to neuroblastoma.

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Philadelphia – Researchers from Children’s Hospital of Philadelphia (CHOP) have developed a method to help cancer immunotherapies reach otherwise “invisible” tumors by helping guide therapies to their appropriate targets. This could be particularly useful for very difficult-to-treat tumors like neuroblastoma. The findings were recently published by the journal [Science Advances](#).

Certain tumors are known as “cold” tumors, meaning that they are not likely to trigger an immune response and therefore more difficult to detect. Immune responses require proteins to present themselves on the surface of tumor cells. Immunotherapies have revolutionized cancer care for certain tumors, but they still require this surface expression to distinguish tumor cells from normal, healthy cells in the body.

Class I human leukocyte antigen (HLA-I) proteins act like barcodes and help tag tumor cells and viruses, and reduced HLA-I surface expression is a hallmark of immune invasion.

The laboratory of [Nikolaos G. Sgourakis, PhD](#), Professor in the [Center for Computational and Genomic Medicine](#) at CHOP and the Department of Biochemistry and Biophysics at the University of Pennsylvania, has been seeking new methods of exploiting HLA-I proteins to help develop new immunotherapies for treating “cold” tumors.

“Neuroblastoma is a classic example of a cold tumor,” Sgourakis said. “Neuroblastomas have low antigen expression, very few mutations, and very poor T-cell infiltration, leading to less effective immunotherapy strategies. It has been an elephant in the room and required a fresh approach to studying the problem.”

In this new study, Sgourakis and his colleagues outline HLA-Shuttle, an engineered protein complex that works by manipulating the machinery that drives HLA-I proteins and how they are expressed. HLA-Shuttle is designed as a chaperone to immunotherapy by restoring antigen presentation in immunologically “cold” neuroblastoma cells.

Importantly, HLA-Shuttle not only has therapeutic potential, it is also able to identify previously unknown or understudied therapeutic targets by bringing them to the surface of tumor cells. In this study, the researchers reported the identification of 180 peptides mapped to 30 genes that could provide new therapeutic windows not just for immunotherapies but other precision medicine approaches to treating tumors.

Thus far, this work has been performed in cell lines outside of the body, so the next critical steps are to make sure the technology can be delivered safely in the body.

Additionally, while this approach has focused on neuroblastoma, the “coldest of cold tumors,” researchers plan to study HLA-Shuttle’s applications in other “cold” tumors, which include pancreatic, ovarian and prostate cancers as well as many sarcomas. Collaborations with labs at CHOP and Penn will determine in which tumors and treatments this technology will be most effective.

“While our focus is on cold tumors, we could definitely use this approach on warmer tumors as well to drastically expand the number of potential therapeutic targets for difficult-to-treat cancers,” Sgourakis said.

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