Technique that characterizes different immune cell groups in individual patients could revolutionize cancer treatments

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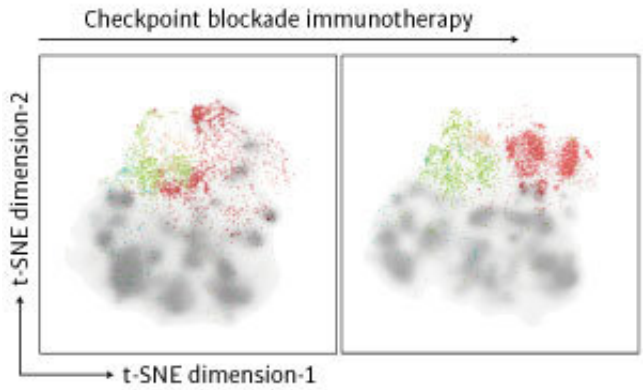

A plot of all the different possible phenotypes of T cells before without (left) vs. with (right) immune checkpoint blockade immunotherapy. The colored dots represent T cells that are tumor neoantigen specific and colored by which tissue they were derived from: (red) tumor, (green) dLN (draining lymphnode - the lymph-node closest to the tumor - peripheral immune tissue), (blue): ndLN (non-draining lymphnode - peripheral immune tissue) and (orange): spleen (peripheral immune tissue). Credit: A*STAR Singapore Immunology Network

A pioneering technique developed by A*STAR researchers can identify and profile specific groups of immune cells that target cancer cells in individual patients. This approach could open the door to personalized cancer treatments.

Cancer cells produce many antigens that trigger immune responses from the body. One group of immune cells called CD8+ cytotoxic T cells recognize and bind to antigens attached to the surface of cancerous cells. Often, mutations unique to individual patients create mutant antigens, or 'neoantigens', which lead to a tumor-specific immune response. Scientists hope to harness these responses to create personalized cancer treatments, and possibly neoantigen-based cancer vaccines.

Now, Evan Newell and co-workers at A*STAR's Singapore Immunology Network, along with scientists at Washington University in St Louis, USA, have developed an approach that can efficiently identify and characterize neoantigen-specific CD8+ T cells in mice. Their technique may help determine whether a tumor will respond to specific immunotherapies.

"In theory, we might predict how someone will respond to certain immunotherapies by looking at the characteristics of the immune cells that are circulating in the patient's blood," explains Newell. "However, this is challenging, because there are huge numbers of circulating cells and only a tiny proportion of them are neoantigen-specific CD8+ T cells."

Newell's team hypothesized that patients who were receptive to effective immunotherapy would have tumor-specific T cells with specific characteristics. The team's technique combines mass cytometry with heavy metal staining to simultaneously screen and profile the multiplicity of such cells in blood and tumor samples.

"Other approaches require that you stimulate the T cells with their specific antigens to identify them," says Newell. "Instead, we used isolated proteins from the antigens called peptide-MHCs (major histocompatibility complex), which the T cell receptors bind to. In addition to formulating the proteins carefully to promote stable

interactions, we labelled them with heavy metals so that they were detectable in high-throughput mass cytometry."

In experiments on mice with sarcoma tumors that responded well to particular immunotherapies, the team analyzed T cells targeting 81 possible tumor antigens. They identified T cells specifically associated with two neoantigens in spleens, tumors and lymph nodes. Depending on the type of immunotherapy used, the neoantigen-specific T cells displayed different phenotypes during treatment, whereas other T cell populations were mostly unaffected.

"It's possible we could identify tumor-specific T cells that could either be expanded and re-infused into patients to boost their immune response, or used as biomarkers to predict responses to any given immunotherapy," says Newell. "Our technique could also identify relevant tumor antigens to develop personalized cancer vaccines."

More information: M. Fehlings et al. Checkpoint blockade immunotherapy reshapes the high-dimensional phenotypic heterogeneity of murine intratumoural neoantigen-specific CD8+ T cells, *Nature Communications* (2017). DOI: 10.1038/s41467-017-00627-z

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