

Role of natural neoantigens in paraneoplastic syndromes and artificially introduced neoantigens in non-paraneoplastic autoimmunity

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Cancers are caused by mutations and cancer cells may continue to mutate. Single base-pair changes in the DNA sequence lead to single amino-acid difference in the resulting proteins, which become a source of neoantigens. T cells with T cell receptors (TCR) that recognize peptides that differ by as little as one amino acid from a self peptide, can be positively selected and migrate to the periphery. These low affinity self reactive (LASR) T cells that barely qualify to be positively selected in the thymus, can have high enough affinity to self peptides to be functional and cause autoimmune disease upon activation. Such LASR T cells are ideally suited to recognize the above neoantigens and have a major role in the immune response against cancer.(1)

The activation of such LASR T cells results in CD8⁺ T cell mediated paraneoplastic syndromes.

Autoimmunity can therefore be a sign of successful immune response against cancer and may indicate good cancer prognosis in some cases.(2) Autoimmunity is also a common side effect of cancer immunotherapy.

Animal proteins have high homology to equivalent human proteins. Animal proteins have many locations where the sequences differ by a single amino acid, compared to equivalent human proteins. Therefore they are an ideal source of neoantigens, just like modified proteins produced by cancer cells. Immunization with vaccines that contain thousands of animal proteins therefore results in a widespread cancer immune response, both cell mediated and humoral. Since most vaccines are administered as intramuscular (IM) or subcutaneous (SC) injections, the skin is the site of priming. T cells that are activated in the skin draining lymph nodes are imprinted with the site of priming. They express skin homing receptors. Therefore, cell mediated autoimmunity is more likely at sites that secrete ligands to skin homing receptors.(3) Autoimmunity at other sites is likely to be caused by vaccine induced autoantibodies.(4)

There are many reports of autoimmune encephalitis following immunization.(5,6)

The increasing use of animal protein containing biologics can also be expected to produce autoimmune disease. Most biologics are produced on Chinese Hamster Ovary (CHO) cells.

Plant proteins have much less homology to human proteins. However, there are still numerous locations in plant protein sequences that have significant sequence alignment to human proteins. Therefore immunization against plant proteins can also result in autoimmunity. This results in numerous food associated autoimmune disorders. (7,8)

On the flip side, animal and plant protein containing vaccines can act as unintended shotgun neoantigen cancer immunotherapy.(9) Perhaps off-label use of such relatively inexpensive, readily available vaccines can be considered for cancer treatment.

References

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