# Antitumor Immunity and Its Evasion by Tumors

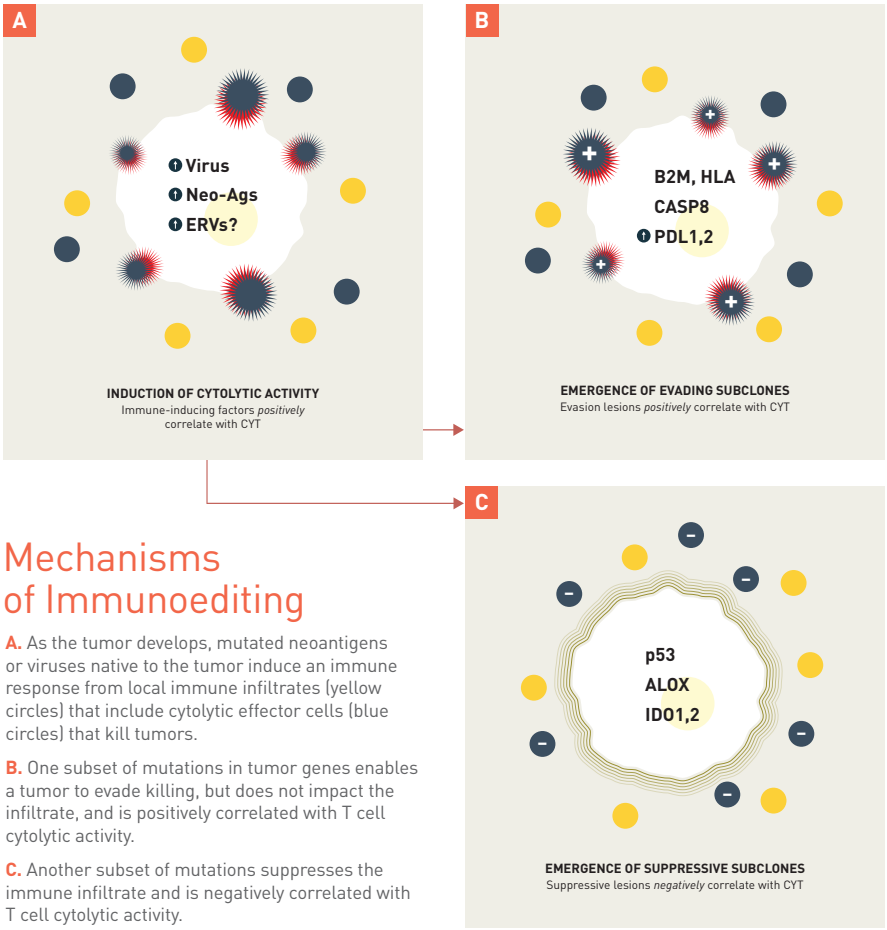
***How do tumors evolve to evade the immune response?***

While some patients with cancer mount a strong immune response against their tumors, most have no significant immune response against these invaders. Little is known, however, about what genetic and environmental factors shape an individual tumor's response to the immune system, or about how the tumor and the immune system interact at a cellular and molecular level.

Nir Hacohen, PhD, director of the Center for Cancer Immunotherapy at Massachusetts General Hospital Cancer Center, and Gad Getz, PhD, director of bioinformatics at Massachusetts General Hospital Cancer Center and Department of Pathology, who directs the Cancer Genome Computational Analysis group at the Broad Institute of MIT and Harvard, have found the first large-scale evidence showing two things. First, mutated peptides that are presented on the surface of human tumors are recognized by T cells, and the tumor cells harboring these mutations are killed by T cells. Second, tumors evolve mutations that confer resistance to the immune system under pressure from killer T cells. Published in the January 15, 2015, issue of *Cell*, the findings show how T cells exert selection pressures on a tumor, influencing its genetic composition and future susceptibility to the immune system.[1] These and related discoveries have already paved the way to novel treatments.

## SELECTION FOR IMMUNE-RESISTANT MUTATIONS IN CANCER

Dr. Hacohen and Dr. Getz analyzed genetic data from thousands of tumor samples across 18 different tumor types sourced from the Cancer Genome Project. They hypothesized that heavy cytolytic activity by T lymphocytes—the cells of the immune system that destroy infected cells and cancer cells—would lead to the killing of tumor cells, and this in turn would put pressure on the tumor to evolve mutations that resist the killing of T cell. Such cytolytic activity was measured by the presence of proteins and enzymes critical to the destruction of target cells.




## Mechanisms of Immunoediting

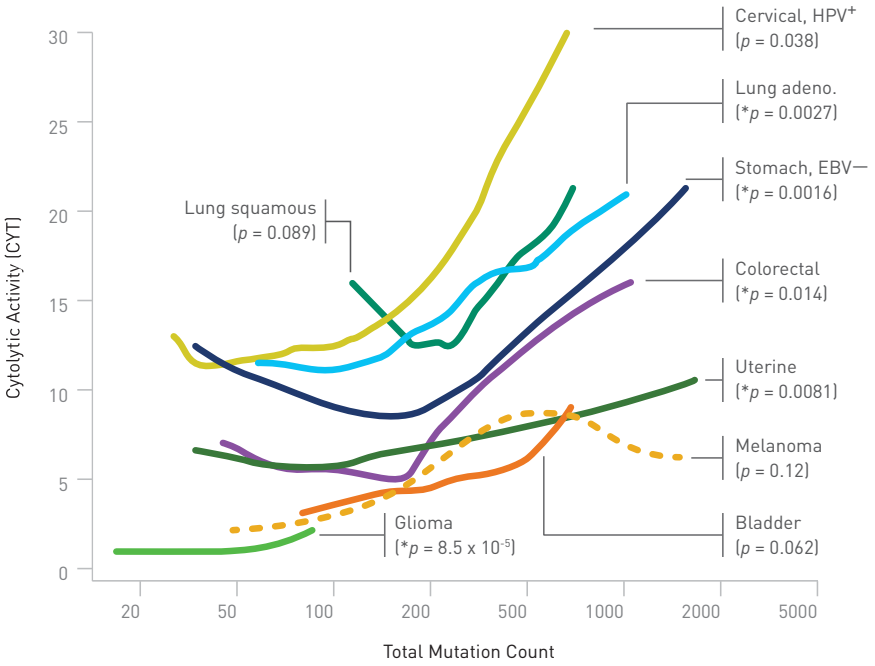
**A.** As the tumor develops, mutated neoantigens or viruses native to the tumor induce an immune response from local immune infiltrates (yellow circles) that include cytolytic effector cells (blue circles) that kill tumors.

**B.** One subset of mutations in tumor genes enables a tumor to evade killing, but does not impact the infiltrate, and is positively correlated with T cell cytolytic activity.

**C.** Another subset of mutations suppresses the immune infiltrate and is negatively correlated with T cell cytolytic activity.

The researchers tested whether the most common 373 genetic mutations found in cancers would be correlated with the T cell cytolytic activity. A correlation indeed existed between high levels of T cell cytolytic activity and some of these mutations, suggesting that the immune system chooses to attack cells with genetic mutations that specifically help a cell evade the immune response. Among these were mutations in the HLA class 1 and B2M genes, which govern a cell's ability to present tumor antigens to T cells. The presentation of tumor antigens normally provokes a T cell attack. However, cells with a mutation that halts their display on the surface, such as HLA and B2M mutations, are protected from the immune system and are thus "positively selected," says Dr. Hacohen.

The researchers explain that the findings offer lessons for immunotherapy. Given the evidence that resistant mutations can arise in response to immunotherapy, therapies and vaccines are best delivered to tumors when they have just begun to grow or have been minimized by surgery, as that is when genetic diversity is at its lowest. "When mutation diversity is lower, there will be less risk of resistance to a vaccine treatment," says Dr. Hacohen. However, the larger the tumor, the greater the genetic diversity, and the greater the opportunity for positive selection for immune-resistant cells.




## Tumor Type and Mutation Count

The table shows that tumors with higher mutation counts provoke a more aggressive immune response.

### TUMOR CELLS HARBORING MUTATED ANTIGENS ARE KILLED BY T CELLS

Additionally, the researchers discovered that the number of mutated peptides, or neoantigens, presented by the tumor cells is lower than the number expected based on the background silent mutation rate of a tumor, which is especially true for colorectal cancer. The finding of fewer neoantigens than expected suggests that the cancer cells whose mutations led to the presentation of neoantigens had been eliminated by the immune response, in a process of negative selection.[2]

While the association between higher mutation load and greater immune activity was consistent with recently published studies showing that higher mutation rate tumors are more susceptible to checkpoint-blockade therapies, says Dr. Hacohen, it was the first time this connection had been confirmed through analysis of genetic data in untreated tumors that undergo spontaneous immunity.

### A ROLE FOR ENDOGENOUS RETROVIRUSES?

On a more surprising note, the study

found that a number of endogenous retroviruses (ERVs)—viruses that live in human cells but are usually silent—are reactivated in certain kinds of tumors. For example, a retrovirus known as ERVE4 is reactivated in clear cell kidney cancer, a kind of cancer that tends to stimulate a strong immune response.

"The more you have of those viruses, the more cytolytic activity you have in that tumor," says Dr. Hacohen. While the researchers could not determine causality—whether the ERVs activate immunity or the inflammation triggers the expression of the ERVs—the ERVs are highly dysregulated in tumors, which could lead them to being used to help activate local immunity in cancer therapies.

## THERAPEUTIC APPLICATIONS

The discoveries have already led to therapeutic applications. Dr. Hacohen and his colleagues have developed a personalized vaccine to target the mutated antigens in individual tumors. The vaccine is in trials in several diseases, including melanoma and glioblastoma, and will soon be tested in several more cancer types.

[1] Rooney, M.S., S.A. Shukla, C.J. Wu, G. Getz, and N. Hacohen, "Molecular and Genetic Properties of Tumors Associated with Local Immune Cytolytic Activity," ***Cell***, Jan 2015: 160, 48–61.

[2] Schreiber, R.D., L.J. Old, and M.J. Smyth, "Cancer Immunoediting: Integrating Immunity's Roles in Cancer Suppression and Promotion," ***Science,*** March 2011, 331: 1565–1570.

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