

Immune Evasion by Merkel Cell Cancer Could Involve Inhibitory Markers

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Merkel cell carcinoma (MCC) is an aggressive neuroendocrine skin cancer resulting in three times higher disease-associated mortality than malignant melanoma. At least 80% of MCC tumors are associated with an oncogenic virus, Merkel cell polyomavirus (MCPyV). Additionally, studies have shown that the chance of survival is significantly lower for immune-suppressed individuals. Viral immune evasion is believed to be at play in the development of this cancer, and researchers in the laboratory of Dr. Paul Nghiem of the Clinical Research Division and the Division of Dermatology at the University of Washington set out to study the potential mechanisms involved.

The researchers utilized multiparameter flow cytometry panels to identify and characterize the immune cells in the blood and tumors of patients with MCC. They found MCPyV-specific T cells in MCC patients, and observed that the cell frequencies correlated with disease burden. This was not the case for T cells specific for other viruses, such as cytomegalovirus or Epstein-Barr virus, which did not seem to fluctuate over time. Having established the presence of virus-specific T cells in the cancers, the researchers next attempted to characterize the T cell phenotype to understand how the cancer could be evading control by the immune system despite the increased presence of these cells.

"How can a tumor grow despite increasing numbers of CD8+ T cells that specifically recognize antigens expressed only in the cancer cells," was the question Dr. Nghiem's group was hoping to address. The researchers looked for markers of activation and markers of T-cell inhibition on the cancer-associated T cells. What they found was that two prominent inhibitory markers, PD-1 and Tim-3, appeared at higher levels on the MCPyV-specific T cells both in the tumor and in the blood compared with T cells specific to other viruses. These markers are known to indicate a state of T cell exhaustion rather than activation (see figure). The authors explored further by analyzing the presence of a ligand to the PD-1 marker (PD-L1) in tumor cells and found that they were spatially associated with the T cells. The formation of the PD-1 receptor / PD-L1 ligand complex is known to transmit inhibitory signals and reduce the proliferation of these T cells.

The positive outcome from the study is that the PD-1 / PD-L1 pathway can be targeted with therapeutics that are in the process of becoming available for clinical applications. The findings that

these immunoinhibitory molecules are strongly involved in MCC immune evasion are highly encouraging. "Because T cell exhaustion appears to be involved in immune evasion by this cancer and should be reversible with therapeutically available agents," says Dr. Nghiem, who is already looking towards the future, "we strongly hope they will be tested soon in clinical trials [for MCC]."

[Afanasiev OK, Yelistratova L, Miller N, Nagase K, Paulson K, Iyer JG, Ibrani D, Koelle DM, Nghiem P. 2013. Merkel Polyomavirus-Specific T Cells Fluctuate with Merkel Cell Carcinoma Burden and Express Therapeutically Targetable PD-1 and Tim-3 Exhaustion Markers. *Clin Cancer Res* 19\(19\):5351-60.](#)

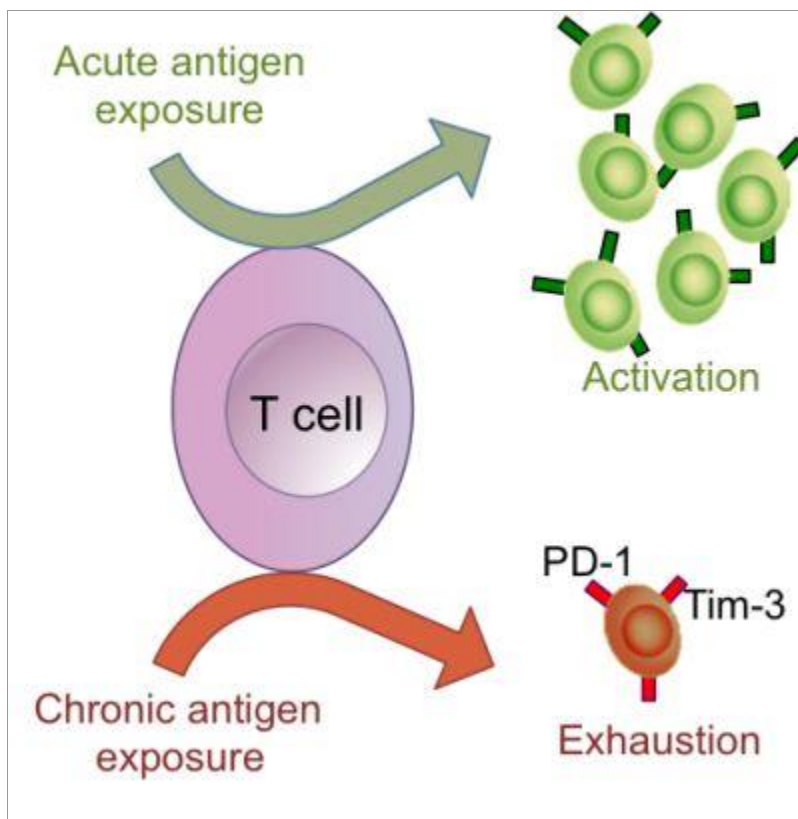


Image provided by Dr. Paul Nghiem.

Markers of T cell exhaustion (PD-1 and Tim-3) were found in T cells associated with MCC tumors. These T cell inhibitory molecules could explain immune evasion by the cancer.