Tumor necrosis factor overcomes immune evasion in p53-mutant medulloblastoma.

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Public Summary:
Many immunotherapies act by enhancing the ability of cytotoxic T cells to kill tumor cells. Killing depends on T cell recognition of antigens presented by class I major histocompatibility complex (MHC-I) proteins on tumor cells. In this study, we showed that medulloblastomas lacking the p53 tumor suppressor do not express surface MHC-I and are therefore resistant to immune rejection. Mechanistically, this is because p53 regulates expression of the peptide transporter Tap1 and the aminopeptidase Erap1, which are required for MHC-I trafficking to the cell surface. In vitro, tumor necrosis factor (TNF) or lymphotoxin-beta receptor agonist can rescue expression of Erap1, Tap1 and MHC-I on p53-mutant tumor cells. In vivo, low doses of TNF prolong survival and synergize with immune checkpoint inhibitors to promote tumor rejection. These studies identified p53 as a key regulator of immune evasion and suggest that TNF could be used to enhance sensitivity of tumors to immunotherapy.

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