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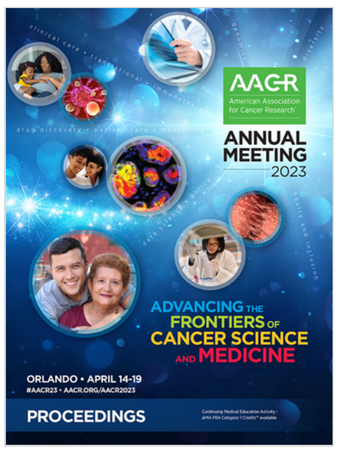

Article Contents

Abstract

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Abstract 5120: NPRL2 gene therapy induces effective antitumor immunity in KRAS/STK11 mutant anti-PD1 resistant metastatic human NSCLC in a humanized mouse model FREE

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Abstract

NPRL2/TUSC4 is a potent tumor suppressor gene whose expression is reduced in many cancers including NSCLC. Restoration of NPRL2 expression in cancer cells induces DNA damages which leads to cell cycle arrest and apoptosis. We investigated the antitumor immune responses to NPRL2 gene therapy on anti-PD1 resistant KRAS/STK11 mutant NSCLC in a humanized mouse model. H1299 cells transfected with NPRL2 showed significant inhibition of colony formation after NPRL2 transfection. Humanized mice were generated by transplanting fresh human cord blood derived CD34 stem cells into sub-lethally irradiated NSG mice. The level of engraftment of human CD45, CD3 T, CD19 B, NK cells was verified before tumor implantation. Mice harboring > 25% human CD45 cells were considered humanized. KRAS/STK11 mutant anti-PD1 resistant A549 NSCLC cells were injected intravenously into humanized NSG mice and developed lung metastasis. Metastases were treated with intravenous injection of NPRL2 gene loaded cationic lipid nanoparticles with or without pembrolizumab (anti-PD1). A dramatic antitumor effect was mediated by NPRL2 treatment, whereas pembrolizumab was ineffective. A significant antitumor effect was also found in non-humanized NSG mice, although the effect was greater in humanized mice suggesting that the possible role of antitumor immunity. The antitumor effect of NPRL2 was associated with increased infiltration of human CD45, CD3 T, cytotoxic T, NK cells, and a decreased number of human regulatory T cells (Treg) in tumors. PD1 expressing exhausted CD8 T cells were downregulated in both the NPRL2 and pembrolizumab groups. The number of activated T cells ($CD69^+CD8^+$T), effector (EM) and central memory (CM) CD8 T cells were significantly increased by NPRL2 treatment. NPRL2 induced antigen presenting HLA-DR^+ dendritic cells. When NPRL2 was combined with pembrolizumab, no synergistic antitumor effect was found in the KRAS/STK11 mutant anti-PD1 insensitive tumors. However, a robust and synergistic antitumor effect was observed in the KRAS wild type, anti-PD1 sensitive H1299 tumors grown in humanized mice treated with NPRL2 + pembrolizumab. Cytotoxic T cells, NK cells, and HLA-DR^+ DC were associated with the antitumor effect. DOTAP-NPRL2 was tested in a syngeneic mouse model with LLC2 tumors that are KRAS mutant and anti-PD1 resistant. Consistent with the A549 humanized mouse model, NPRL2 showed a significantly strong antitumor effect whereas anti-PD1 was not effective in this model. The antitumor effect of NPRL2 was again correlated with the upregulation of HLA-DR^+ DC, CD11c DC, TILs, NK and downregulation of Treg and myeloid cells in the tumor microenvironment. Taken together, these data suggest that NPRL2 gene therapy induces antitumor activity on KRAS/STK11 mutant anti-PD1 resistant tumors through DC mediated antigen presentation and cytotoxic immune cell activation.

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