NK and T cells, and IFN-γ are required for the anti-tumor efficacy of combination-treatment with NKG2A and PD-1/PD-L1 checkpoint inhibitors in preclinical models

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Background

Monalizumab (IPH2201) is a first-in-class humanized IgG4 targeting NKG2A, which is expressed as a heterodimer with CD94 on subsets of NK cells, γδ T cells and tumor infiltrating CD8+ T cells. This inhibitory receptor binds to HLA-E in humans and to Qa-1b in mice. Monalizumab blocks binding of CD94-NKG2A to HLA-E, reducing inhibitory signaling and thereby enhancing NK and T cell responses.

PD1/PD-L1 inhibitors are successfully being used to treat patients with a wide variety of cancers. Combined blockade of NKG2A and PD-1 receptors on tumors infiltrating NK and CD8+ T cells of untreated mice. Analysis performed by flow cytometry on day 22 after A20 tumor cell s.c. engraftment (n>8 mice).

Mechanism of action

Monalizumab (IPH2201) is a first-in-class humanized IgG4 targeting NKG2A. This inhibitory receptor binds to HLA-E in humans and to Qa-1b in mice. HLA-E is frequently up-regulated on cancer cells, protecting from killing by NKG2A+ cells. Monalizumab blocks binding of CD94-NKG2A to HLA-E, reducing inhibitory signaling and thereby enhancing NK and T cell responses.

Qa-1 expression is induced in vitro by IFN-γ and in vivo after tumor cell engraftment in mice

Anti-tumor efficacy of anti-NKG2A/anti-PD-1 combination is mediated by NK cells and CD8+ T cells and IFN-γ

Combination of durvalumab and monalizumab increases secretion of IFN-γ in SEB assay and is dependent on IFN-γ pathway

Conclusions

Together, these data indicate that blocking NKG2A in conjunction with PD-1/PD-L1 checkpoint blockers provides increased anti-tumor efficacy by a mechanism that depends on IFN-γ. These data strengthen the rationale for assessing this combination in clinical trials.