NKG2A immune checkpoint blockade potentiates cetuximab induced ADCC in head and neck cancer preclinical model

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Background

Monalizumab (Iph2201) is a first-in-class humanized IgG targeting NKG2A (Natural Killer Group 2A), which is expressed as a heterodimer with CD94 on subsets of NK cells, y6 T cells and tumor infiltrating CD8+ T cells. This inhibitory receptor binds to HLA-A (Human Leukocytes Antigen-E) molecules which are frequently upregulated on cancer cells providing a negative regulatory signal to tumor-infiltrating lymphocytes (TILs). Monalizumab blocks binding of CD94/NKG2A to HLA-E, reducing inhibitory signaling and thereby unleashing NK and T cell responses.

High expression of EGFR (epidermal growth factor receptor) occurs in most epithelial malignancies and particularly in squamous cell carcinoma of the head and neck (SCCHN) and is associated with poor prognosis. The anti-EGFR monoclonal antibody cetuximab (Ctx) is thought to act through blocking oncogenic signaling and by inducing Fc receptor-mediated antibody dependent cell cytotoxicity (ADCC) which involves human NK cells.

Here, we investigated ex vivo and in vitro the rationale of combining monalizumab with Ctx in the treatment of head and neck cancers.

Mechanism of Action

SCCHN tumor are infiltrated by CD8+ T cells expressing CD94/NKG2A in head and neck cancer patients

Conclusions

- SCCHN are infiltrated by NK and CD8+ T cells expressing CD94/NKG2A.
- TN tumor cells express HLA-E.
- NKG2A blockade enhances cetuximab-mediated ADCC towards HN tumor cell lines in a dose-dependent manner.
- Altogether, these data support the rationale for investigating monalizumab in SCCHN patients and in combination with cetuximab in clinical trials (NCT02643550; see poster CT158).