

Cytotoxic Function of Human Natural Killer Cells is Inhibited by Transforming Growth Factor beta (TGFβ)

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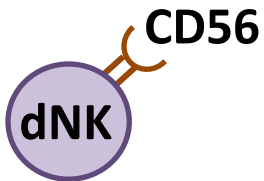
Abstract:

Natural killer (NK) cells have tumor destructive ability. Inconsistent with this function, NK cells found in kidney tumors are poorly cytotoxic. Similarly, pregnancy-associated NK cells lack cytotoxicity due to TGF β exposure. We demonstrate that NK cells cultured with TGF β lose the ability to effectively kill kidney cancer cells.



Introduction: Classes of Natural Killer cells

Pregnancy

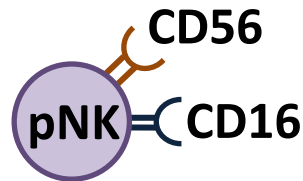


Decidual NK (dNK) cells
CD56⁺/CD16⁻

Promote

- Angiogenesis
- Healthy Pregnancy
- Importantly, DO NOT KILL

Circulation (Blood)

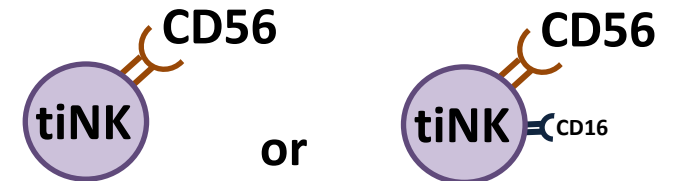


Peripheral NK (pNK) cells
CD56⁺/CD16⁺ (~95%)

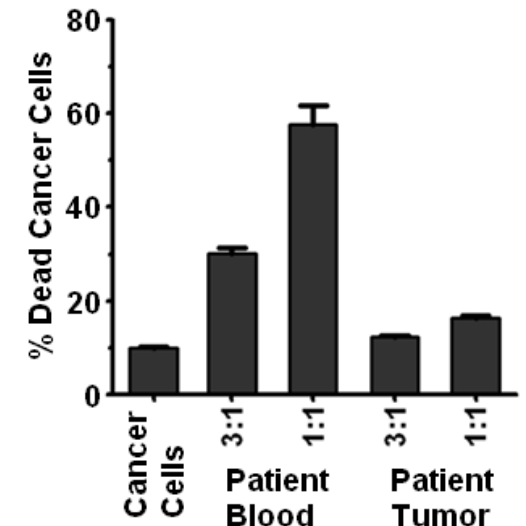
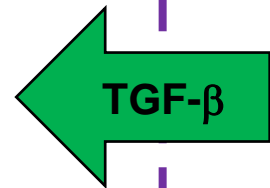
Kill

- Cells infected by bacteria & viruses
- Cancer (neoplastic) cells
- Absence of self antigens (MHC)

Tumor

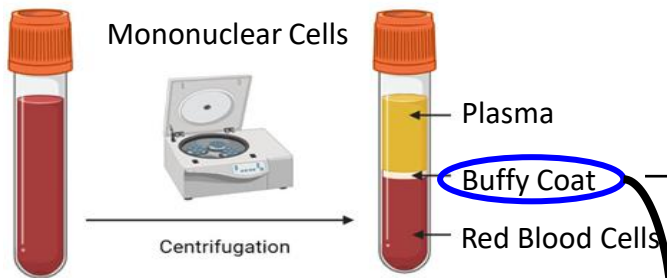


Tumor Infiltrating NK (tiNK)
CD56⁺/CD16⁻ or CD56⁺/CD16^{dim}

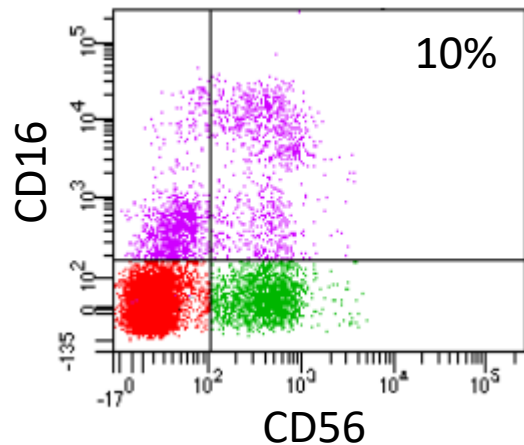


Methods: NK Cell Isolation and Flow Cytometry for TGFβ receptors

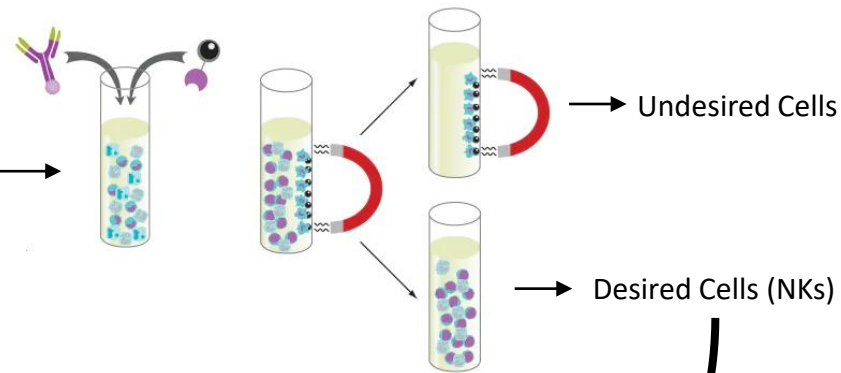
Density Centrifugation



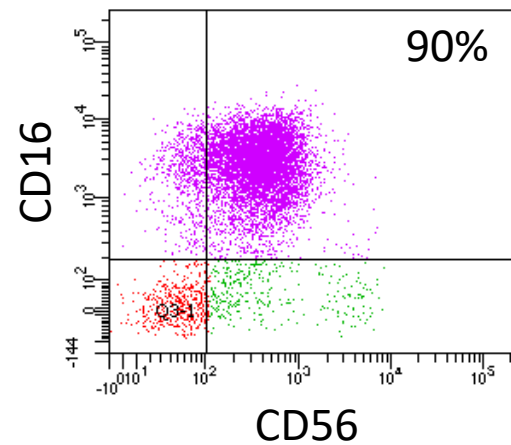
CD56⁺/CD16⁺ Cells
in Blood Sample



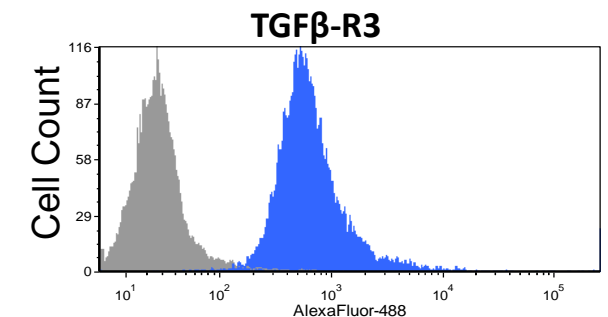
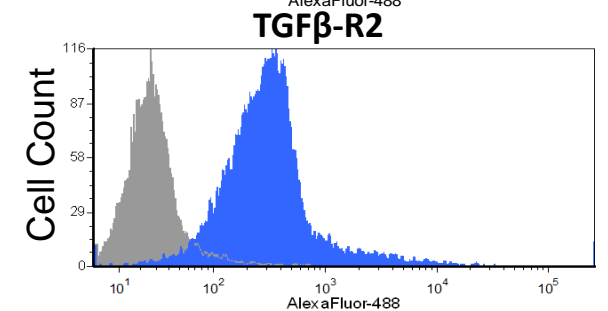
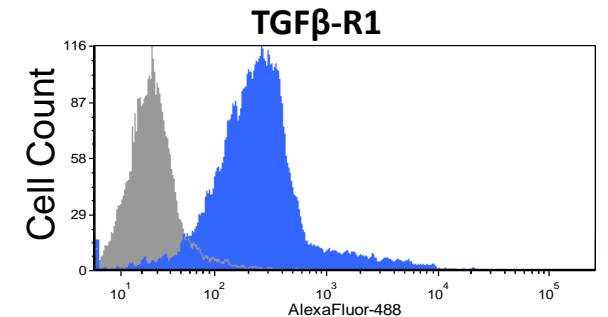
Negative Selection



Isolated NK Cells from
Blood Sample

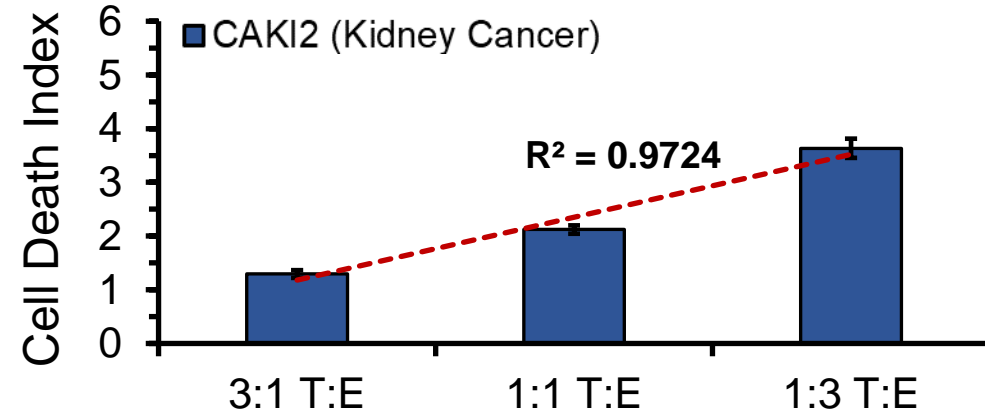
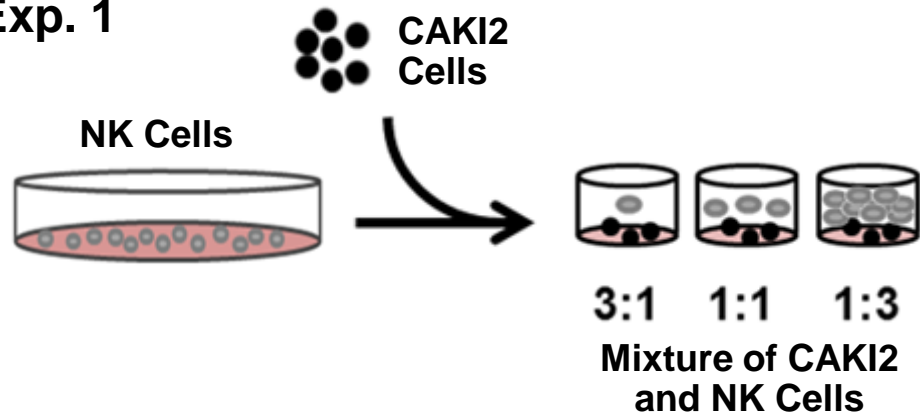


Cell with no TGFβ-R antibody (Negative Control) Cells with TGFβ-R antibody bound

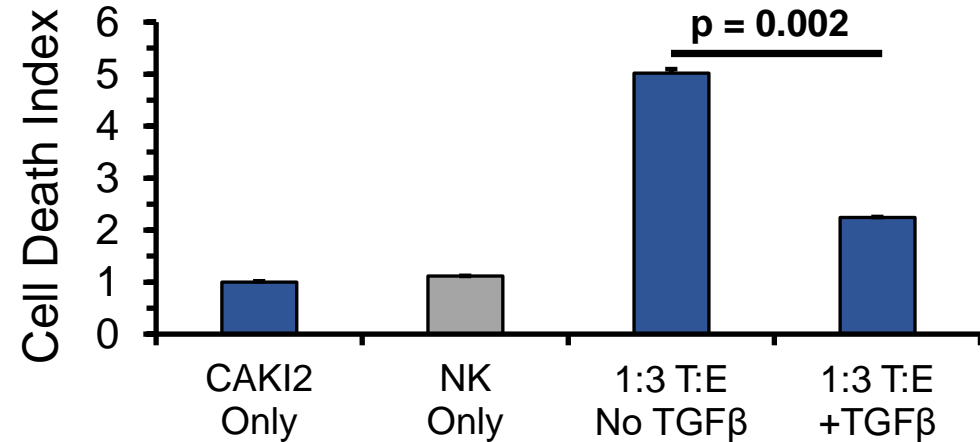
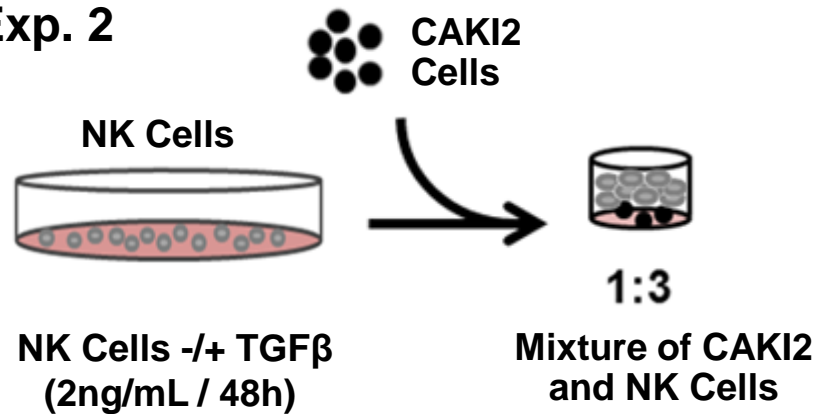


Results: NK Cell Cytotoxicity is Inhibited by TGFβ

Exp. 1



Exp. 2



Conclusions and Future Directions:

Conclusions

- Human NK cells express all three TGF β receptors (R1, R2, R3)
- TGF β is a potent inhibitor of NK cell cytotoxicity against CAKI2 kidney cancer cells

Future Directions

- Can the inhibitory effect of TGF β be blocked by a small molecule inhibitor (SD208; R&D Systems), TGF β -specific antibody, or by inhibition of tumor TGF β transcription (pirfenidone; Genentech)?
- What gene expression changes are associated with TGF β -mediated inhibition of NK cell function?
- Do TGF β -treated NK cells promote early tumor-growth *in vivo* and can this function be reversed by pre-treatment with TGF β inhibitors?

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