Tumor-infiltrating lymphocytes (TIL) with inducible and membrane-bound IL-12 exhibit superior anti-tumor activity in vitro

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Background

- Tumor-infiltrating lymphocytes (TIL) cell therapy has shown clinical benefit for patients with solid tumors.
- However, an immunosuppressive tumor microenvironment (TME) may abrogate the full potential of TIL.
- The presentation of cytokine (c)IL-12 increases to improve TIL therapy.
- Engineered TIL secreting IL-12 was disrupted when cell-cell interaction was blocked with a transwell, indicating a lack of IL-12 shedding.
- TeIL-12 shows a good safety profile with minimal shedding of IL-12; however, NFAT-TeIL-12 demonstrates the potential for a better safety profile due to less shedding of IL-12 relative to TeIL-12 in co-culture systems.

Methods

- Tissues from several solid tumor histologies including non-small cell lung cancer, breast cancer, head & neck cancer, and ovarian cancer were fragmented and cultured for 11 days (pre-rapid expansion protocol [pre-REP])
- The tumor tissue cultures were then transduced with a lentivirus containing a gene encoding membrane-bound IL-12.
- Engineered TIL secreting IL-12 showed clinical benefit, although circulating IL-12–related AEs limited its clinical application.
- Tissue from several solid tumor histologies including non-small cell lung cancer, breast cancer, head & neck cancer, and ovarian cancer were fragmented and cultured for 11 days (pre-rapid expansion protocol [pre-REP]).

Results

- Engineered TIL secreting IL-12 showed clinical benefit, although circulating IL-12-related AEs limited its clinical application.
- Engineered TIL secreting IL-12 demonstrated a good safety profile with minimal shedding of IL-12; however, NFAT-TeIL-12 demonstrated the potential for a better safety profile due to less shedding of IL-12 relative to TeIL-12 in co-culture systems.
- TeIL-12/NFAT-TeIL-12 TIL show reduced TIM-3 and TIGIT expression compared to Mock pLV-ctrl TeIL-12 TIL.
- KILR-THP-1 cytotoxicity assay shows enhanced cytotoxic activity of TeIL-12/NFAT-TeIL-12 TIL.

Conclusions

- Both TeIL-12 and NFAT-TeIL-12 show superior in vitro cytotoxic activity with pronounced PD-1 inhibition; superior tumor cytotoxicity was maintained after repeated TransACT stimulation.
- Both TeIL-12 and NFAT-TeIL-12 show a favorable T cell phenotype with increased expression of CD38 and decreased expression of TIM-3 and TIGIT.
- TeIL-12 shows a good safety profile with minimal shedding of IL-12; however, NFAT-TeIL-12 demonstrates the potential for a better safety profile due to less shedding of IL-12 relative to TeIL-12 in co-culture systems.
- Engineered TIL secreting IL-12 demonstrate the potential for a better safety profile due to less shedding of IL-12 relative to TeIL-12 in co-culture systems.

References

1. Zhang Y, Gilbert N, Innamarato P, et al. Engineered TIL secreting IL-12 demonstrate the potential for a better safety profile due to less shedding of IL-12 relative to TeIL-12 in co-culture systems.

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