Synthetic tumour-infiltrating interleukin(IL-12) for targeted and tolerable immunotherapy reduces metastasis in pancreatic cancer

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Background

- Pancreatic Ductal Adenocarcinomas (PDACs) are highly collagenous with an immunosuppressive tumour microenvironment. They rely on proteases for metastatic and angiogenic potential1.
- The use of pro-inflammatory interleukin 12 (IL-12) is limited by toxicity and poor infiltration in solid tumours2.
- Conjugation of a Collagen-Binding Domain (CBD) to IL-12 is promising in solid tumours but toxicity could be further reduced3.
- Masking CBD-IL12 through a protease-sensitive linker allows for tumour-specific drug activation4.

Research question

Does masking CBD-IL12 render the molecule less toxic and more efficacious at suppressing pancreatic tumour burden?

Methodology

- Collision and Sadanandam5 PDAC subtypes were analyzed for protease gene expression.
- Masked CBD-IL12 was produced in HEK 293F cells and purified using immobilized metal affinity and size exclusion chromatography.
- The linker cleavage was assayed using Western blotting.
- Masked CBD-IL12 was tested in vivo in a PDAC and colorectal mouse model.

Results - Masked CBD-IL12 reduces tumour burden

- Figure 2: Masked CBD-IL12 reduces MC38 tumour burden.

Results - Masked CBD-IL12 is cleaved by PDAC and liver metastases

- Figure 3: MMP9, MMP2 and PLAU gene expression analysis in Collision and Sadanandam5 PDAC subtypes. These proteases cleave the linker.

Conclusions

The masked CBD-IL12 linker is preferentially cleaved by tumour lysate due to abundant proteases.
- Masked CBD-IL12 therapy suppressed MC38 tumour burden and considerably reduced liver metastases in the mesenchymal murine PDAC model.

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Disclosures

The first/narrating author does not have any conflicts of interest to declare.

References


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Figure 2: Schematic of the structure of CBD-IL-12 and masked CBD-IL-12

Figure 3: Western blot of IL-12 following incubation of masked CBD-IL-12 with tissues/serum. mCIL12 = masked CBD-IL-12

Figure 4: Western blot of IL-12 following incubation of masked CBD-IL-12 with tissue/liver. mCIL12 = masked CBD-IL-12

Figure 5: Hematoxylin and eosin staining of whole liver sections of mice bearing mesenchymal PDAC tumours.