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Harnessing innate immunity in cancer therapies: The example of natural killer cell engagers

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Background

Most immunomodulatory approaches have focused on enhancing T-cell responses, by immune checkpoint inhibitors, chimeric antigen receptor T cells or bispecific antibodies. Although these therapies have led to exceptional successes, only a minority of cancer patients benefit from these treatments, highlighting the need to identify new cells and molecules that could be exploited in the next generation of immunotherapy. Given the crucial role of innate immune responses in immunity, harnessing these responses opens up new possibilities for tumor control. Antibody engineering provides us with great opportunities to induce synthetic immunity by harnessing the biological functions of innate immune cells, in particular by boosting the capacity of Natural Killer (NK) cells to kill tumor cells directly and to stimulate T-cell responses indirectly.

Methods

We designed NK cell engagers (NKCEs) to optimize NK cell antitumor functions by binding to three activating receptors, NKp46, CD16 and IL-2R, on NK cells, and one antigen on tumor cells. The IL-2R interacting element is a variant of interleukin-2 (IL-2v) unable to bind the α-subunit of its receptor to limit regulatory T cell activation and IL-2Rα-mediated toxicity.

Results

In vitro, NKCE-IL2v promoted IL-2R signaling preferentially in NK cells, inducing primary human NK cell proliferation and cytolytic activity, and the secretion of cytokines and chemokines only after binding to the tumor target. In mouse models of both invasive and solid tumors, NKCE-IL2v induced NK cell proliferation and accumulation at the tumor bed, and had a higher anti-tumor efficacy than approved therapeutic antibodies targeting the same tumor antigen. Mechanistically, incorporating NKp46-, CD16- and IL-2 receptor-binding moieties in the same molecule, was essential for strong activity. In non-human primates, CD20-directed NKCE-IL2v resulted in sustained CD20+ B-cell depletion with minimal systemic cytokine release and no clinical sign of toxicity.

Conclusions

Tetrafunctional NKCE-IL2v thus constitutes a synthetic technological platform combining the induction of NK cell proliferation and effector functions without toxicity, supporting its clinical development for next-generation cancer immunotherapies.

Legal entity responsible for the study

Innate Pharma.

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Disclosure

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