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Heterodimeric Fc-fused IL12 elicits antitumor effects by generating memory CD8+ T cells

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Statement of the Problem: Interleukin-12 (IL12) (p35/p40 complex) is a heterodimeric cytokine with potent anti-tumor activity. However, its short serum half-life and high dose-related toxicities limit its clinical efficacy.

Methodology & Theoretical Orientation: In this study, we exploited heterodimeric Fc technology to develop mono-mIL12-Fc, which presents mIL12 in the naturally occurring heterodimeric form with an Fc-mediated extended serum half-life. We constructed heterodimeric Ig Fc-fused IL12 in the naturally occurring heterodimeric form of IL12, termed mono-mIL12-Fc, in which the p35 and p40 subunits were fused to the N-terminus of two different Fc variants, respectively. We also generated Fc-fused bivalent IL12 with two IL12 units (bi-mIL12-Fc) by fusion of scIL12 (p40-linker-p35) to the N-terminus of wild-type Fc as a control.

Findings: Mono-mIL12-Fc exhibited a much longer plasma half-life than recombinant mIL12, enabling twice-weekly systemic injections to remove established tumors in syngeneic mouse models. Mono-mIL12-Fc was more potent than wild-type Fc-based bivalent-binding IL12-Fc (bi-mIL12-Fc) for eradicating large established immunogenic tumors without noticeable toxicities by enhancing interferon-gamma production and the proliferation of immune effector cells in tumors. More importantly, mono-mIL12-Fc triggered weaker IL12 signaling than bi-mIL12-Fc, favoring the generation of functional and protective memory $CD8^+$ T cells. Notably, our study illustrates that mono-mIL12-Fc triggers modest pSTAT4 activation and T-bet expression in effector $CD8^+$ T cells, resulting in a switch from T-bet to Eomes activation for the differentiation into MPECs and eventually long-lived memory $CD8^+$ T cells. However, the strong IL12 signaling mediated by bi-mIL12-Fc drives effector $CD8^+$ T cells into terminally differentiated SLECs, thereby excluding the development of MPECs.

Conclusion & Significance: Our results demonstrate that heterodimeric-Fc-fused IL12 is a suitable format for augmenting adaptive $CD8^+$ T cell immune responses, providing a practical alternative to the systemic administration of IL12 for anti-tumor therapy.

Biography

Jung-Eun Kim has expertise in cancer immunotherapies. Aims to elucidate how antibodies and cytokines modulate immune cells that infiltrate tumor through quantitative and qualitative assessment of immune cells in syngeneic mouse tumor models. Research is focused on cellular immune mechanisms of T lymphocytes activation and regulatory T cells suppression. Team also investigates rationales for combination of therapeutic antibodies targeting tumor cells and/or immune-checkpoint receptors. Their research will lead to the next generation of immune-based therapies in human cancer.

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