Hyleukin-7, the Fc-fused interleukin-7, generates anti-tumor activity by modulating both adaptive and innate immune cells in the tumor microenvironment

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Abstract

Interleukin-7 (IL-7), a strong candidate for a novel immunotherapeutic agent, plays important roles in the development and homeostasis of T lymphocytes. Recently IL-7 has shown positive effects in various models by increasing cells in both mice and humans; however, the short half-life and stability of recombinant IL-7 has remained a challenge for its clinical application to cancer immunotherapy. Here, we investigated the anti-tumor effects of clinical stage, long-acting form of recombinant human IL-7 fused with hybrid Fc (rhIL-7-hyFc), Hyleukin-7 in mice. rhIL-7-hyFc administration in tumor-free mice generated cytokine-induced CD8+ T cell proliferation which activated T cell homeostasis by expanding Teffector type CD8+ T cells displaying activation-induced attributes, such as Eomes, Granzyme B, CXCR3, and IFN-\(\gamma\). Upon injected into mice with syngeneic tumor grafts, rhIL-7-hyFc reduced antitumor activity in a dose-dependent manner. rhIL-7-hyFc dramatically expanded CD8+ T cells in the periphery and released cytokines that induce tumor, leading to a high CD8+ T cell-to-tumor ratio in the tumor microenvironment (TME). rhIL-7-hyFc increased CD8+ and granzym B (Gzm B) expression but decreased expression of inhibitory immune checkpoint molecules on CD8+ tumor-infiltrating lymphocytes (TILs). Strikingly, rhIL-7-hyFc reduced myeloid-derived suppressor cells (MDSCs) in the TME, resulting in a TME favorable. Collectively, rhIL-7-hyFc treatment confers anti-tumor activity by inducing a "CD8+ T cell infiltrated-inflamed-immune favorable" TME. Furthermore, we found that the anti-tumor activity of rhIL-7-hyFc was achieved under lymphopenic conditions by normalizing CD8+ T cell homeostasis. In sum, rhIL-7-hyFc generates antitumor activity by inducing a CD8+ T cell infiltrated-inflamed-immune favorable TME. Additionally, the combination treatment of rhIL-7-hyFc with cyclophosphamide (CPA) and immune checkpoint blockade showed enhanced antitumor efficacy in an advanced tumor model. Furthermore, we found that the antitumor activity of rhIL-7-hyFc was achieved under lymphopenic conditions by normalizing CD8+ T cell homeostasis. In sum, rhIL-7-hyFc generate an effective anti-tumor response through reconstituting CD8+ T lymphocytes; this activity was highly enhanced by combination therapies with chemotherapeutics and immune checkpoint blockade. Our data suggests that rhIL-7-hyFc can be applied to various cancer immunotherapy regimens as a monotherapy or in combination with conventional and other immunotherapies.

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Conclusions

rhIL-7-hyFc treatment induces cytokine-induced T cell proliferation and activation

Combination of rhIL-7-hyFc significantly enhances antitumor efficacy of the immunochemotherapy

rhIL-7-hyFc therapy combined with anti-PD-1 induces effective antitumor response under lymphopenic condition

Summary

- rhIL-7-hyFc after CPA T cell homeostasis through the cytokine-induced cell activation and proliferation.
- Antitumor efficacy of rhIL-7-hyFc is mediated by dominant tumor infiltration of CD8+ T cells and the exhaustion of a ‘CD8+ T cell-influenced-immune favorable’ tumor microenvironment.
- Combination treatment with rhIL-7-hyFc significantly enhances antitumor efficacy of immunochemotherapy.
- Antitumor activity of rhIL-7-hyFc is also achieved under lymphopenic conditions through combined immunotherapy.