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Interleukin-10: An Immune-Activating Cytokine in Cancer Immunotherapy

Hui Zhang, *First Affiliated Hospital, China Medical University, Shenyang, People's Republic of China*
Yu Wang, *Duke University Medical Center, Durham, NC*
E. Shelley Hwang, *Duke University Comprehensive Cancer Center, Durham, NC*
You-Wen He, *Duke University Medical Center, Durham, NC*

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In the accompanying article, Naing et al[1] report encouraging clinical results from a phase I trial of single-agent pegylated recombinant human interleukin-10 (IL-10) in the treatment of advanced refractory solid tumors. IL-10 has often been considered an immunosuppressive cytokine because of its association with multiple regulatory or suppressive immune-cell populations, such as regulatory $CD4^+$ and $CD8^+$ T cells, B10 cells, myeloid-derived suppressive cells, and tolerogenic dendritic cells, as well as its powerful inhibition on antigen presentation and immune-cell activation.[2,3] Further supporting this notion is the observed strong correlation between circulating IL-10 levels and poor prognosis of various patients with cancer.[3] However, there is also abundant preclinical and clinical evidence supporting an antitumor activity of IL-10. For example, it was found that mice lacking IL-10 or IL-10 receptor are susceptible to tumor development,[4-6] and exogenous IL-10 can boost antitumor immunity in mice.[5,7-10] The antitumor effect of IL-10 is likely a result of its stimulating activity on $CD8^+$ T cells as it promotes the differentiation and expansion of effector $CD8^+$ T cells.[11-14] Several studies from tumor animal models have suggested that IL-10 directly expands $CD8^+$ tumor-infiltrating T cells (TILs) to kill tumor cells in vivo.[5,8,9,15] Indeed, contrary to the reported correlation between circulating IL-10 levels and poor prognosis among patients with cancer,[3] $CD8^+$ T cells expressing IL-10 are associated with a favorable prognosis in patients with lung cancer.[16] These seemingly contradictory results raise a major question: Is systemic use of IL-10 immune suppressive or activating in patients with cancer? Because systemic IL-10 would act on all assessable IL-10 receptor–positive cells, the overall effect of pegylated recombinant human IL-10 on parenteral administration could be either pro- or antitumor.

The Naing et al[1] study provides strong evidence that IL-10 is an immune-activating cytokine in patients with advanced solid tumors. In all 24 patients treated with active dose of AM0010 at 20 to 40 μg/kg, the serum levels of proinflammatory cytokines IL-18 and interferon gamma (IFN-γ as well as the Th2 cytokine IL-4 were dramatically increased. In contrast, the serum level of the immune-suppressive cytokine transforming growth factor beta was decreased in these patients (Fig 1A). Most importantly, the patients treated with the active dose had an overall response rate of 21%, a strong indication of clinical antitumor activity of recombinant IL-10 in vivo. Given the pleotropic effects of IL-10 on many types of cells, a major concern with systemic IL-10 application is its toxicity and tolerability. Clinical use of anticancer cytokines such as IL-2 and IFNs has been limited by their toxicity.[17] The Naing et al[1] study shows an acceptable safety profile of pegylated recombinant human IL-10 with prolonged clinical use. Although patients treated with AM0010 experienced grade 3 to 4 treatment-related adverse events (AEs), all treatment-related AEs seemed to be manageable and were reversed on temporary dose interruption or reduction. Even more encouraging is that no immune-related AEs were observed in any treated patients, paving the way for combinatorial therapy with other immune-targeting agents, such as immune checkpoint inhibitors anti–programmed death-1 (PD-1)/PD-1 ligand (PD-L1) and anti–cytotoxic T-cell lymphocyte-4 (CTLA-4).[18]

The results from this phase I trial[1] provide a solid foundation for future phase II to III trials to address several important questions. First, what types of cancers and subpopulations of patients will respond to systemic IL-10 treatment? Among 15 patients with advanced renal cell cancer (RCC) with a median of three prior therapies, there was an impressive 27% objective response rate, compared with a similar 25% objective response rate achieved in patients with RCC treated with anti–PD-1 nivolumab.[19] The fact that one of five patients with non–small-cell lung cancer and one of four patients with melanoma also achieved partial response suggests broad suitability of IL-10 treatment, although the small sample sizes require that these data be interpreted with caution. As with all other cancer therapies, careful selection of patients responding to IL-10 treatment will be critical for precision therapy. Elevated serum levels of IL-18, IFN-γ and IL-4 may serve as a useful readout for IL-10–induced immune activation in patients, but they are not sufficient for preselection of responding patients on the basis of the presented data.[1] Notably, several patients showed mixed responses, with substantial reduction in some lesions and increase in others. On the basis of the evidence showing direct effect of IL-10 on $CD8^+$ TILs in situ,[5,8,9,15] one may wonder whether the mixed responses in those patients resulted from different infiltrating levels of antitumor $CD8^+$ TILs in the various lesions within the same patients. We speculate that the degree of tumor tissue

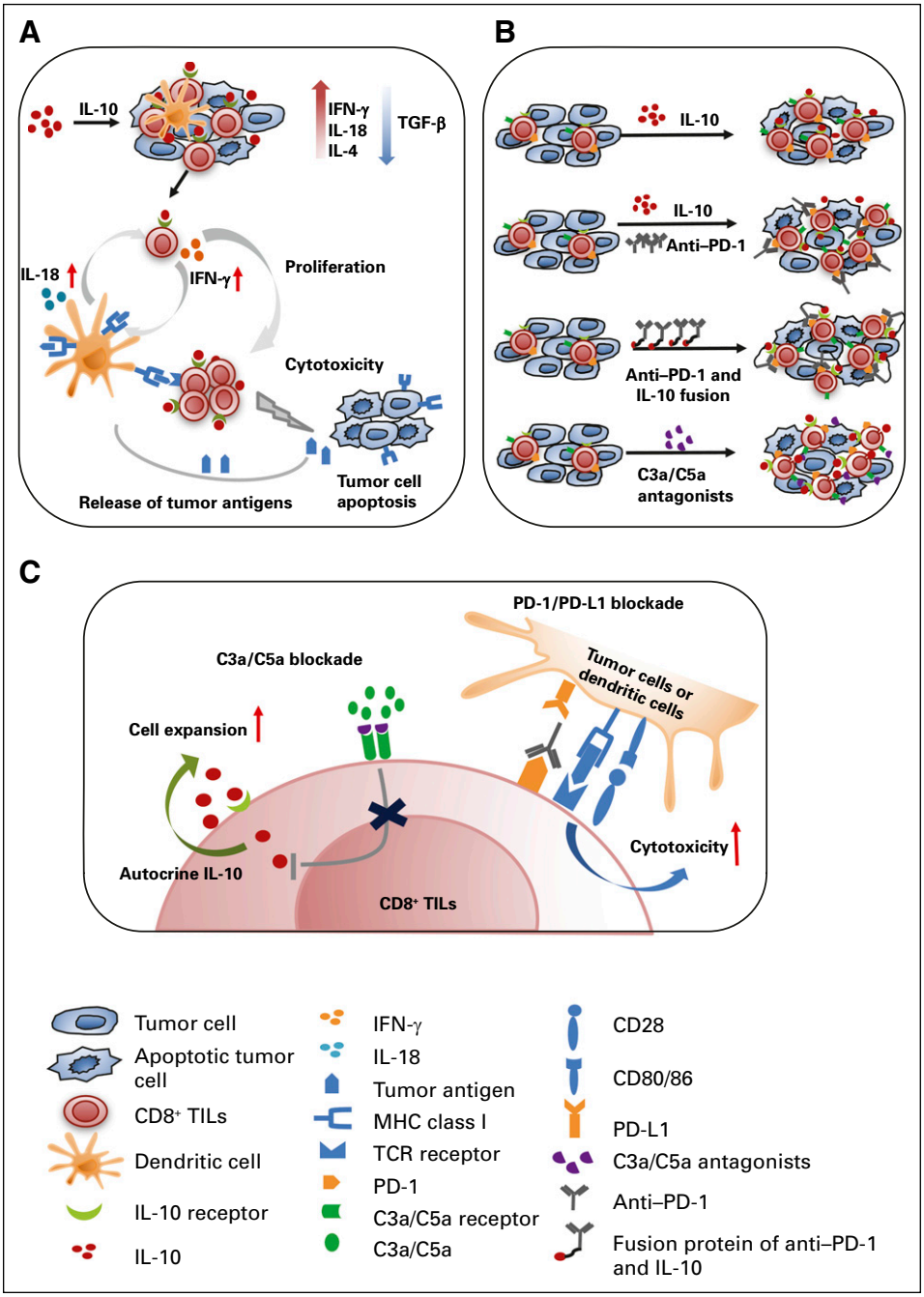

Fig 1. (A) Systemic interleukin-10 (IL-10) administration dramatically increases levels of interferon gamma (IFN-γ), IL-18, and IL-4 but reduces transforming growth factor beta (TGF-β) level in patients with solid tumors. IL-10 leads to increased secretion of IFN-γ by activated $CD8^+$ tumor-infiltrating T cells (TILs), which further induces IL-18 production from dendritic cells. The positive feedback loop of IFN-γ and IL-18 signaling accelerates $CD8^+$ TILs expansion. Meanwhile, IFN-γ enhances expression of major histocompatibility complex (MHC) class I molecules on tumor and dendritic cells, facilitating tumor-cell cytotoxicity of $CD8^+$ TILs. (B) Combinatorial treatment approach provides an improved means of antitumor strategy. IL-10 injection alone enhances $CD8^+$ TIL antitumor activity; combination of IL-10 and anti–programmed death-1 (PD-1) treatments potentially improve the antitumor activity of IL-10 monotherapy; fusion protein of anti–PD-1 and IL-10 delivers IL-10 specifically to antitumor $CD8^+$ TILs, which may further improve efficacy of both immunotherapeutic agents. C3a/C5a antagonists facilitate antitumor activity of $CD8^+$ TILs by promoting IL-10 secretion. (C) Different modes of antitumor activity by C3a/C5a antagonists and anti–PD-1. C3a/C5a blockade exerts antitumor activity through enhancing autocrine IL-10 production from $CD8^+$ TILs. C3a/C5a antagonists block C3a/C5a-mediated inhibition of IL-10 production from $CD8^+$ TILs. Autocrine IL-10 then promotes $CD8^+$ TIL expansion. While anti–PD-1 blocks inhibitory signals from PD-1 ligand (PD-L1), it removes the brake on activated $CD8^+$ TIL–mediated killing and then improves T-cell cytotoxicity.

infiltration by $CD8^+$ T lymphocytes may be a useful biomarker to predict response to systemic IL-10 therapy.

Second, how are we to improve the clinical efficacy of IL-10 treatment in patients with solid tumors? An important observation from the Naing et al[1] study comes from patients who had received prior immunotherapy: Two patients with RCC for whom prior IL-2 treatment had failed and one with melanoma for whom prior anti–CTLA-4 treatment had failed experienced partial responses with IL-10 therapy. This result suggests that IL-10–mediated antitumor activity differs from that mediated by IL-2 or anti–CTLA-4 in patients with advanced solid tumors. A recent study also suggested that IL-10–mediated antitumor activity is independent of the PD-1/PD-L1 pathway.[15] Thus, combinations of IL-10 with US Food and Drug Administration–approved immunotherapeutic agents offer new means of improving the antitumor activity of IL-10 monotherapy (Fig 1B). Although both IL-10 and anti–PD-1 monoclonal antibodies target $CD8^+$ TILs, their functional mechanisms are different: anti–PD-1 removes the brake on antitumor cytotoxic T-cell lymphocyte killing by blocking inhibitory signals from PD-L1, whereas IL-10 provides fuel to amplify antitumor cytotoxic T-cell lymphocyte killing by promoting effector expansion. Thus, generating a fusion protein comprising anti–PD-1 and IL-10 to deliver IL-10 specifically to antitumor $CD8^+$ TILs may further improve the efficacy of both immunotherapeutic

agents while avoiding the regulatory effect of IL-10 on off-target cells (Fig 1C).

Can antitumor $CD8^+$ TILs be induced to produce IL-10 by themselves so that autocrine IL-10 will directly promote their tumor killing? The answer is yes. Antitumor $CD8^+$ TILs do not routinely produce IL-10, because production is inhibited by complement-mediated suppression through complement receptors C3aR and C5aR.[15] When complement signaling is blocked, $CD8^+$ TILs produce IL-10 and exert potent tumor-killing activity (Fig 1B).[15] Thus, C3aR and C5aR expressed on $CD8^+$ TILs are considered a novel class of immune checkpoint receptors that could be targeted in combination with the current immune checkpoint inhibitors for cancer immunotherapy (Fig 1C). In summary, the Naing et al[1] study provides promising results on the clinical application of pegylated recombinant human IL-10 in the treatment of advanced solid tumors. Although single-agent IL-10 treatment is unlikely to result in durable responses in most refractory solid tumors, this study suggests new avenues for cancer immunotherapy. Further research on the use of combinatorial treatments based on our emerging knowledge of the immune response to tumor cells has enormous potential to improve response to such therapies while limiting off-target effects.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: You-Wen He
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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E. Shelley Hwang
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