Arsenic/Interferon α-induced selective eradication of leukemia-initiating activity in adult T cell leukemia: Loss of interleukin-10 and activation of innate immune microenvironment response

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Background:
ATL is a chemotherapy-resistant malignancy with dismal prognosis and patients with ATL exhibit an immunosuppressed profile. Arsenic trioxide (AS) and interferon-α (IFN) selectively trigger Tax degradation and apoptosis in ATL cells and cures *Tax*-driven murine ATL. In chronic ATL patients, the combination of AS/IFN and zidovudine induces complete remission associated with a sharp decrease of IL-10 and a significant increase of IL-2 and IFN-γ, hence restoring an immunocompetent profile.

Objectives:
We previously reported that AS/IFN mediates leukemia initiating cells (LIC) eradication curing murine *Tax*-driven ATL. We investigated the molecular basis of AS/IFN-induced ATL LIC clearance.

Methods:
ATL SCID mice were injected with *Tax* transgenic cells, and subsequently treated with AS/IFN from day 18 until day 21 post-leukemic cells inoculation (Primary ATL mice) before sacrifice. Spleen-derived cells from these mice were injected into secondary recipient SCID mice that were left untreated and sacrificed weekly for molecular assessment, or were treated with mouse recombinant IL-10 protein. To evaluate the potency of anti-IL10 therapy, primary ATL SCID mice were treated with anti-IL-10 monoclonal antibodies.

Results:
AS/IFNα-induced abrogation of LIC activity requires IL-10 expression shutoff. Loss of IL-10 secretion drives production of inflammatory cytokines by the microenvironment, followed by macrophage and natural killer cells immune-mediated clearance of ATL LICs. Critically, recombinant IL-10 rescued ATL LIC activity, whereas anti-IL10 monoclonal antibodies sharply decreased ATL growth. The triple combination of AS/IFN with anti-IL-10 monoclonal antibodies significantly prolonged survival of ATL SCID mice and abrogated LIC activity.

Conclusion:

AS/IFN-induced abrogation of ATL LIC activity is secondary to a decreased production of interleukin-10, increased production of inflammatory cytokines, and activation of innate immunity. These results emphasize the sequential and dual targeting of malignant ATL cells and their immune microenvironment in leukemia initiating cell (LIC) eradication and provide a strong rational to test AS/IFNα/anti-IL10 combination in ATL patients.

Disclosure of Interest Statement:
None

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