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TARGETING IDO1 AND ATP CATABOLISM OVERCOMES THE TOLEROGENIC EFFECTS OF CYTARABINE ON ACUTE MYELOID LEUKEMIA IMMUNE MICROENVIRONMENT

D. Ocadlikova[1], P. Portararo[2], E. Adinolfi[3], E. De Marchi[3], A. Pegoraro[3], E. Orioli[3], S. Sangaletti[2], A. Curti[1]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [2]Fondazione IRCCS, Istituto Nazionale dei Tumori; [3]Department of Medical Sciences, University of Ferrara, Italy

Introduction: In solid tumors, chemotherapy not only exerts direct cytotoxic effect but also modulates immune response through the release of damage-associated molecular patterns such as ATP. Although chemotherapy remains the therapeutic backbone for acute myeloid leukemia (AML) patients, its effect on immune microenvironment have been poorly investigated. We previously demonstrated that the release of extracellular ATP and its metabolites by chemotherapy-treated AML cells shapes antitumor immunity by influencing the activity of dendritic cells (DCs) and regulatory T cells (Tregs). Here, we further investigated in different murine AML models the impact of ATP signaling and its catabolism on the leukemia immune microenvironment following chemotherapy.

Methods: WT and P2X7R KO BALB/c mice were injected with WEHI-3B AML cells. Cytarabine (Ara-C) was administered on days 9 and 11 post-AML cell injection. At sacrifice, tumors were analyzed for infiltrating DCs and Tregs by flow cytometry, and single-cell RNA sequencing was performed. For combination therapy experiments, intra-bone injections of B/6-derived C1498 AML cell lines were used.

Results: Preliminarily, Ara-C treatment paradoxically reduced survival probability of mice injected with AML by promoting AML engraftment and dissemination. This effect was totally abrogated in immunodeficient and nude mice, supporting an immunosuppressive effect of Ara-C. Single-cell RNA sequencing of immune microenvironment supported this hypothesis by revealing the up-regulation of tolerogenic genes and pathways associated with regulatory DCs and Tregs in Ara-C treated mice. Flow-cytometry analysis confirmed that Ara-C treatment resulted in a significant increase of both mature tolerogenic DCs co-expressing indoleamine 2,3-dioxigenase 1 (IDO1) and the ATP ectonucleotidases CD39 and CD73 and IL-10-producing Tregs. Their frequency was higher in mice exhibiting reduced responsiveness to Ara-C. Notably, enrichment of $IDO1^+$ CD11chigh DCs and $IL\text{-}10^+$ Tregs was not observed in the P2X7R KO model, suggesting that both IDO1 expression in DCs and IL-10 production in Tregs depend on ATP release and subsequent catabolism. Consistently, CD39 and CD73 ectonucleotidases were expressed on $IDO1^+$ CD11chigh DCs and $IL\text{-}10^+$, but not on $IL\text{-}10^-$ Tregs. Therapeutically, Ara-C combined with anti-IDO1 and anti-CD73 inhibitors markedly reduced the frequency of $CD11^+MHC^+CD39/CD73^+IDO1^+$ DCs and $IL\text{-}10^+CD73^+$ Tregs compared with Ara-C monotherapy, resulting in better disease control and enhanced survival.

Conclusions: Chemotherapy may promote the induction of tolerogenic immune microenvironment through ATP–IDO1–dependent activation of regulatory DCs and Tregs in AML. These findings provide a strong mechanistic rationale for combining immunotherapy such as anti-IDO1 and anti-CD73 with chemotherapy to counteract or disrupt such tolerogenic mechanisms, thereby restoring effective antitumor immune responses.