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Targeted inhibition of myeloid-derived suppressor cells in the tumor microenvironment by low-dose doxorubicin to improve immune efficacy in neuroblastoma

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Abstract

Background: High agglomeration of myeloid-derived suppressor cells (MDSCs) in neuroblastoma (NB) impeded therapeutic effects. This study aimed to investigate the role and mechanism of targeted inhibition of MDSCs by low-dose doxorubicin (DOX) to enhance immune efficacy in NB.

Methods: A total of 250 bagg albino (BALB/c) mice were used as tumor-bearing mouse models by injecting Neuro-2a cells, and MDSCs were eliminated by DOX or dopamine (DA) administration. Tumor-bearing mice were randomly divided into 2.5 mg/kg DOX, 5.0 mg/kg DOX, 50.0 mg/kg DA, and control groups according to a random number table. The optimal drug and its concentration for MDSC inhibition were selected according to tumor inhibition. NB antigen-specific cytotoxic T cells (CTLs) were prepared. Tumor-bearing mice were randomly divided into DOX, CTL, anti-ganglioside (GD2), DOX+CTL, DOX+anti-GD2, and control groups. Following low-dose DOX administration, immunotherapy was applied. The levels of human leukocyte antigen (HLA)-I, CD8, interleukin (IL)-2 and interferon (IFN)-γ in peripheral blood, CTLs, T-helper 1 (Th1)/Th2 cytokines, perforin, granzyme and tumor growth were compared among the groups. The Wilcoxon two-sample test and repeated-measures analysis of variance were used to analyze results.

Results: The slowest tumor growth ($F = 6.095$, $P = 0.018$) and strongest MDSC inhibition ($F = 14.632$, $P = 0.001$) were observed in 2.5 mg/kg DOX group. Proliferation of T cells was increased ($F = 448.721$, $P = 0.000$) and then decreased ($F = 2.047$, $P = 0.186$). After low-dose DOX administration, HLA-I ($F = 222.489$), CD8 ($F = 271.686$), Thl/Th2 cytokines, CD4+ and CD8+ lymphocytes, granzyme ($F = 2376.475$) and perforin ($F = 488.531$) in tumor, IL-2 ($F = 62.951$) and IFN-γ ($F = 240.709$) in peripheral blood of each immunotherapy group were all higher compared with the control group (all of P values < 0.05). The most significant increases in the aforementioned indexes and the most notable tumor growth inhibition were observed in DOX+anti-GD2 and DOX+CTL groups.

Conclusions: Low-dose DOX can be used as a potent immunomodulatory agent that selectively impairs MDSC-induced immunosuppression, thereby fostering immune efficacy in NB

Biography

Dr. Wei Li Xu works in the department of Pediatric Surgery at The Second Hospital of Hebei Medical University, China.