MicroRNA-494 activation overcomes the drug resistance of acute myeloid leukemia cells mediated by bone marrow stromal cells

Chen Tian[1], Yizhuo Zhang[1]

Authors' Affiliations:

[1]Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, 300060, People's Republic of China

Corresponding Authors: Professor Yizhuo Zhang, Department of Hematology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center of Cancer, Key Laboratory of Cancer Prevention and Therapy; E-mail: yizhuozhang111@163.com

Running Title: role of microRNA-494 in AML

Abstract

Acute myeloid leukemia (AML) is a malignant and aggressive disease not sensitive to chemotherapy partially because of the protection from mesenchymal stromal cells (MSCs). Our previous studies found that MSC could protect AML cells from apoptosis through c-Myc dependent pathway. But the regulation of c-Myc in AML cells mediated by MSC is still unknown. To elucidate the mechanism, we performed microRNA array analysis of AML cell lines and validated by Taqman realtime PCR. The results showed that the expression of miR-494 in AML cells after coculture with MSC were down-regulated. Reporter gene analysis confirmed miR-494 as one of the regulators of c-Myc. In the coculture system, activation of miR-494 in AML cells induced proliferation suppression and apoptosis of AML cells in vitro. After addition of mitoxantrone to the coculture system, the proliferation of AML cells with miR-494 activation was suppressed greater than control cells. After subcutaneous injection of AML cell lines with MSC, the tumor growth was suppressed in miR-494 overexpression group. And the tumor formation was even smaller after treatment of mitoxantrone in the miR-494 overexpressing group. Moreover, miR-494 activation resulted in decreased circulating leukemic cell counts in peripheral blood and bone marrow and prolonged survival in a xenotransplant mouse model injecting with miR-494+ AML cellls and MSCs compared to control mouse model. Our results indicate that miR-494 plays an important role in the protection of AML cells by down-regulation of c-Myc through interaction with MSC and miR-494 acts as a potential therapeutic target.

Key words: acute myeloid leukemia, mesenchymal stromal cells, microRNA-494, c-

Myc