

Role and Mechanism of Adenosinergic Axis Involved in the Formation of Myelosuppressive Immune Microenvironment in MDS Patients

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Abstract

Background: Myelodysplastic syndrome (MDS) is a group of malignant hematopoietic stem/progenitor cell clonal disorders. It is characterized by varying degrees of peripheral blood cytopenias, bone marrow inefficiency and pathological hematopoiesis, with a high risk of transformation to acute myeloid leukemia (AML). Previous studies have shown that immune dysfunction and bone marrow microenvironmental disorders are one of the important pathogenic mechanisms of MDS, for which there is still a lack of effective therapeutic approaches. Adenosine is an important metabolic regulator and a key immune checkpoint modulator, which is associated with tumor evasion from the host immune system. Recent studies have suggested that extracellular adenosine (eADO) is a suppressor of immune function, and its main source is the sustained degradation of eATP, which can be sequentially catabolized to eADO via CD39 and CD73, and binds to adenosine receptors on the surface of the cell membrane. Adenosine receptor A2a (A2aR) is the major subtype expressed predominantly in most immune cells. A2aR stimulation usually provides various types of immunosuppressive signals. **Objective:** In vitro experiments were performed to study the inhibitory effect of the adenosinergic axis on immune cell function, to delve into the role and mechanism of this pathway in the immunosuppressive bone marrow microenvironment of MDS, and to reveal its potential clinical value for the treatment of MDS through immune targeting. **Method:** Primary MDS patients, primary AML patients and normal control bone marrow of different risk levels were selected and adenosine concentration in the patients' bone marrow supernatants was measured using ELISA. Flow cytometry was used to detect the expression of CD39, CD73 and A2aR on the cell surface of each component of bone marrow from MDS patients, AML patients and healthy controls, respectively, and to confirm the target cells where the key molecules of the adenosinergic axis are located. An in vitro co-culture system was established to inhibit each key molecule using monoclonal antibodies or inhibitors to analyze their restorative effects on the bone marrow immune microenvironment. **Result:** In the bone marrow of MDS and AML patients, CD39 is highly expressed on CD34+ cells, CD73 is highly expressed on BMSC, and A2aR is highly expressed on NK cells and correlates with disease progression. Inhibition of each target had a restorative effect on the bone marrow immune microenvironment of MDS patients, with the A2aR inhibitor having a more pronounced effect, and RNAseq showed that it might be related to the inhibition of the FoxO pathway, which had been validated by western-blot. **Conclusion:** High adenosine expression in the bone marrow microenvironment of MDS patients, blocking the targets of the adenosinergic axis, especially A2aR, can restore the function of the bone marrow immune microenvironment of MDS patients, and provide effective targets that can be referred to for subsequent treatment of MDS.

Keywords

MDS, Bonemarrow Microenvironment, Adenosine, CD39