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603.LYMPHOID ONCOGENESIS: BASIC

E3 Ubiquitin Ligase TRIM21 Enhances Macrophage-Mediated Bortezomib Resistance By Inducing M2 Polarization in Multiple Myeloma

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Background: Multiple myeloma (MM) is a malignant plasma cell hematologic tumor with an increasing incidence and has become the second most common hematologic malignancy after non-Hodgkin lymphoma. Macrophage is an abundant component of the MM bone marrow microenvironment and contributes to the enhancement of MM drug resistance. Our previous study found that the expression of the E3 ubiquitin ligase TRIM21 was reduced in MM cells, and MM cells with low expression of TRIM21 showed reduced sensitivity to Bortezomib (Bort). This study aims to investigate the role and mechanism of TRIM21 in macrophage-mediated MM Bort resistance.
Objective : Explore the effect and mechanism of TRIM21 in mediating multiple myeloma Bortezomib resistance.
Methods :1. Immunofluorescence to analyze the expression of TRIM21 on macrophages in bone marrow biopsy specimens from patients with MM; 2. QPCR, western blot (WB) and flow cytometry (FCM) to detect the level of macrophage polarization markers after constructing overexpression or knockdown of TRIM21; 3. WB and FCM to detect the sensitivity of MM cells to Bort after co-culture of MM cells and macrophage; 4. Transcriptome sequencing to identify TRIM21-mediated pathway changes in macrophage; 5. QPCR and WB to verify the effect of TRIM21 on macrophage polarization after treatment with pathway inhibitors.
Results:1. Immunofluorescence analysis showed increased expression of TRIM21 in macrophage from relapsed and refractory MM (RRMM) patients compared to newly diagnosed multiple myeloma (NDMM) patients;2. QPCR, WB and FCM results showed that overexpression of TRIM21 in macrophage led to decreased polarization markers of M1 phenotype and increased the polarization markers of M2 phenotype. In contrast, knockdown of TRIM21 increased M1 polarization and decreased M2 polarization; 3. WB and FCM results demonstrated that co-culture of MM cells with TRIM21-overexpressing macrophages significantly enhanced MM cell tolerance to Bortezomib and decreased MM cell apoptosis; 4. Transcriptome sequencing revealed activation of the JAK-STAT3 pathway in macrophages after TRIM21 overexpression; 5. QPCR and WB results showed that the macrophage polarization effect induced by TRIM21 overexpression was reversed after treatment with the STAT3 inhibitor C188-9.
Conclusions: Our study shows that TRIM21 is overexpressed in macrophages in patients with relapsed and refractory MM. In addition, TRIM21 induces M2 polarization by activating the JAK-STAT3 pathway, thereby enhancing the protective effect of macrophage on MM cells. These findings provide a new insight into the role of TRIM21 in MM drug resistance and lay an important theoretical foundation for targeting macrophages in MM.
Key words: TRIM21, Macrophage, Bortezomib, JAK-STAT3

Disclosures No relevant conflicts of interest to declare.

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