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ORAL ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Multiple Myeloma with 1q Gain/Amplification Shows Reduced CD38 Expression Via IL-6R Overexpression

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Background: The anti-CD38 monoclonal antibody daratumumab (Dara) significantly improves the outcomes of patients with multiple myeloma (MM). However, chromosome 1q21 gain/amplification (1q+) has been reported to be associated with poor outcomes in patients with relapsed/refractory MM treated with Dara. A recent subgroup analysis of the MAIA study showed that 1q amplification was associated with poor prognosis, even in newly diagnosed patients (Moreau et al. ASH 2022). However, the underlying mechanism of this resistance remains unclear.

Aim and Methods: To elucidate the mechanism of Dara resistance in 1q+ MM cells, we focused on CD38 regulation in 1q+ MM. We examined CD38 expression in primary MM cells of 89 patients with newly diagnosed MM. CD38 expression levels were determined as the mean fluorescence intensity (MFI) using flow cytometry (FCM). FCM was performed using the DURAClone RE PC antibody panel on a Navios cytometer, and the data were analyzed using Kaluza analysis software. The CD38 MFI was assessed in the neoplastic plasma cell population (CD38+/CD138+/CD56+ or CD56−/CD19−). The presence of 1q+ was evaluated using interphase fluorescence *in situ hybridization* (iFISH) in CD138-purified bone marrow plasma cells with a 30% cutoff. Patients with three copies of 1q21 were defined as having a 1q gain, whereas patients with at least four copies were defined as having a 1q amplification. For functional analysis, we employed three human myeloma cell lines (HMCLs) with 1q+ (H929, MOLP8, and MM.1S) and three HMCLs with 1q wild type (WT) (KMS12BM, SKMM2, and NCU-MM1).

Results: We found that 1q+ MM cells showed significantly lower CD38 expression than 1q WT MM cells in our primary samples. Furthermore, we found that isolated 1q+ MM without other high-risk cytogenetic abnormalities showed significantly lower CD38 expression than 1q WT MM. We also found that patients with 1q amplification had significantly lower CD38 expression than those with 1q gain.

To elucidate the mechanism of CD38 downregulation, we focused on the IL-6 receptor (IL-6R) located on chromosome 1q21 because IL-6-mediated JAK/STAT activation has been shown to regulate CD38 expression. Indeed, as the copy number of 1q increased, the expression of IL-6R also increased in our primary samples. Using published datasets, we also confirmed that 1q21 status is closely associated with IL-6R levels. Furthermore, a significant negative correlation was observed between IL-6R and CD38 expression. Based on these results, we hypothesized that IL-6R overexpression due to 1q gain/amplification contributes to CD38 downregulation in 1q+ MM.

To investigate this hypothesis, we first examined the levels of IL-6R in the six HMCLs and verified that 1q+ HMCLs expressed higher levels of IL-6R than 1q WT. We treated these HMCLs with IL-6 and confirmed that only 1q+ HMCLs showed CD38 downregulation. CD38 expression was also downregulated in the primary 1q+ MM samples treated with IL-6 but not in 1q WT samples. Moreover, higher IL-6R expression was observed in 1q+ primary samples than in 1q WT primary samples. IL-6 also led to the robust upregulation of p-STAT3 in HMCLs with 1q+ but not in HMCLs with 1q WT. Particularly, p-STAT3 expression was robustly enhanced in 1q amplification HMCLs that highly expressed IL-6R. Conversely, p-STAT3 expression was minimal in NCU-MM1 cells expressing little or no IL-6R. We also confirmed that IL-6R and STAT3 expressions were significantly and positively correlated in our primary samples and public datasets. Finally, CD38 expression was recovered by treating the 1q+ HMCLs and primary 1q+ MM samples with ruxolitinib (a JAK1/JAK2 inhibitor) or tocilizumab (an anti-IL-6R antibody).

Conclusion: Overexpression of IL-6R in 1q+ MM leads to CD38 downregulation through the activation of the JAK/STAT pathway. This may be associated with the reduced efficacy of Dara in patients with 1q+ MM. Ruxolitinib and tocilizumab can potentially restore CD38 expression by suppressing this pathway, thereby enhancing the effects of Dara on 1q+ MM.

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