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Multiple myeloma with 1q gain/amplification exhibits reduced CD38 expression via interleukin-6 receptor overexpression

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Summary

Multiple myeloma (MM) with chromosome 1q21 gain/amplification (1q+) has been reported to respond poorly to daratumumab. We aimed to explore the mechanism of daratumumab resistance in 1q+ MM. Our findings revealed significantly lower CD38 expression in patients with 1q+ MM than in those with 1q wild type (WT) MM. Next, we focused on the interleukin-6 receptor (IL6R) located in the 1q21 region because a previous report shows that interleukin-6 (IL-6) reduces CD38 expression via the IL-6/Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway activation in MM. Indeed, IL6R expression was significantly higher in 1q+ MM than in 1q WT MM. We verified that the 1q+ human myeloma cell lines (HMCLs) expressed higher IL6R levels than the 1q WT HMCLs. IL-6 treatment induced CD38 downregulation in both the 1q+ HMCLs and primary bone marrow (BM) samples but not in their 1q WT HMCLs and BM samples. IL-6 also resulted in the upregulation of phosphorylated STAT3 in 1q+ HMCLs but not in the 1q WT HMCLs. Furthermore, inhibition of the IL-6/JAK/STAT pathway by treatment with ruxolitinib or tocilizumab restored CD38 expression in the 1q+ HMCLs and BM samples. These findings elucidate the mechanisms underlying daratumumab resistance in 1q+ MM and provide insights for future therapeutic strategies.

KEYWORDS
CD38, chromosome 1q gain, daratumumab, IL-6/JAK/STAT pathway, multiple myeloma

INTRODUCTION

Multiple myeloma (MM) is a complex and multifaceted haematological malignancy characterised by the uncontrolled proliferation of abnormal plasma cells in the bone marrow (BM). In recent years, daratumumab (Dara), an anti-CD38 monoclonal antibody, has significantly improved the outcomes of patients with relapsed/refractory multiple myeloma (RRMM) and newly diagnosed multiple myeloma (NDMM).[1–4] As CD38 is highly expressed in plasma cells, CD38-targeted therapy has been proven to be highly effective in MM treatment. Dara not only eradicates tumour cells through its cytotoxic activity mediated by antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis and complement-dependent cytotoxicity (CDC)[5,6] but also activates tumour immunity mediated by T cells through a reduction in the regulatory T cells that express high levels of CD38.[7,8]

Recently, a chromosomal abnormality of 1q gain/amplification (1q+) was defined as a prognostic factor in the second revised international scoring system.[9] 1q+ is present in 40% of NDMM cases and appears to be a secondary abnormality that emerges in tandem with disease progression.[10,11] The positivity rate reportedly increases upon recurrence.[10] Many

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reports have indicated 1q+ to be associated with a poor prognosis.[12–18] MM cases with three copies of chromosome 1q are referred to as 1q gain, whereas those with four or more copies are termed as 1q amplification (1q amp). Several studies have suggested that MM with 1q amp has a poorer prognosis than MM with 1q gain.[11,17,18] Interestingly, numerous candidate driver genes of MM have been identified on chromosome 1q.[19–24] Thus, a variety of pathological conditions arising from these genetic amplifications converge to develop resistance to therapies. However, many mechanisms underlying the development of resistance to proteasome inhibitors and immunomodulatory drugs are still unclear.

Among these, the impact of 1q+ on the efficacy of Dara also remains controversial. Several reports have suggested that 1q+ MM may be resistant to Dara in RRMM, NDMM and amyloid light chain (AL) amyloidosis settings.[25–29] The latest subgroup analysis update of the MAIA study also revealed that the group with isolated 1q amp did not demonstrate a significant prolongation of the progression-free survival (PFS) (median follow-up duration was 64.5 months) with Dara, lenalidomide and dexamethasone (Dara-Rd).[30] However, the mechanisms underlying this resistance remain unclear. This study aimed to explore the mechanism of Dara resistance in 1q+ MM.

MATERIALS AND METHODS

Patients

In total, 89 patients with NDMM treated at the Kameda Medical Center from October 2017 to September 2021 were included. Patients from whom sufficient ribonucleic acid (RNA) could be extracted were included in this study. All the patients were diagnosed with symptomatic MM according to International Myeloma Working Group criteria 2.0.[31] Cytogenetic abnormalities, including t(4;14), t(14;16), del(17p), t(11;14), del(13q) and 1q gain/amp, were examined in all the patients using interphase fluorescence in situ hybridisation, which was performed according to the protocols for the manufacturer at the Special Reference Laboratory (Hachioji, Tokyo, Japan), using BM plasma cells purified by CD138-coated magnetic beads (Miltenyi Biotec, Bergisch Gladbach, Germany). Samples with three copies of 1q were identified as MM with 1q gain, and those with more than three copies of 1q were identified as MM with 1q amp if they constituted more than 30% of all tumour cells.[32] MM with isolated 1q+ was identified when the MM cells exhibited only 1q+ and no other chromosomal abnormalities. Among the t(11;14)-positive primary samples, we defined samples in which more than 25% of all myeloma cells exhibited lymphoplasmacytoid morphology as immature phenotype MM, as previously reported.[33–35] Lymphoplasmacytoid morphology was defined as reduced cytoplasm cases (nuclear–cytoplasmic ratio exceeding 0.6).[33,36] To validate CD38 downregulation by treatment with interleukin-6 (IL-6), seven samples from patients with NDMM were examined.

Flow cytometric analysis

The CD38 and CD138 expression levels in MM cells from 89 patients were determined by flow cytometry (FCM) as mean fluorescence intensities (MFIs), which were performed using the DURAClone RE PC antibody panel on a Navios cytometer (Beckman Coulter, Brea, CA, USA), and data were analysed using the Kaluza analysis software (Beckman Coulter). For human myeloma cell lines (HMCLs), the CD38 and interleukin-6 receptor (IL6R) expression levels were determined as MFI via FCM using FACSLyric (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). To validate CD38 downregulation in the other four primary samples after treatment with IL-6, the CD38 levels were determined as MFI using FACSMelody (Becton, Dickinson and Company). The FCM data were analysed using FlowJo (Becton, Dickinson and Company).

Statistical analysis

Mann–Whitney *U*, Kruskal–Wallis, Fisher's exact and Student's *t*-tests were used to examine significance. Correlations between variables were identified using the Spearman rank correlation coefficient. *p*-values <0.05 were considered statistically significant. All the statistical analyses were performed using R ver. 4.0.3 and GraphPad Prism 8 software (GraphPad Prism Software Inc., San Diego, CA, USA). Asterisks (*) indicate statistical significance: *$0.01 \le p < 0.05$; **$0.001 \le p < 0.01$; ***$p < 0.001$; ns—not significant.

RESULTS

CD38 expression is reduced in patients with 1q+ MM

Characteristics of the 89 patients with NDMM are shown in Table 1. We first considered the lack of an additive effect of Dara in 1q+ MM to be attributed to the lower CD38 expression levels in 1q+ MM than in 1q wild type (WT) MM. Lower CD38 expression levels may be one of the most important reasons for the reduced efficacy of Dara, as it inhibits the successful triggering of CDC.[37] Therefore, we initially compared the CD38 expression levels between the 1q+ and 1q WT groups in 89 primary samples. Although a trend towards lower CD38 expression levels was observed in the 1q+ group, the difference was not significant (Figure 1A). However, we previously reported that approximately half of the MM cases exhibiting t(11;14) demonstrated reduced CD38 expression levels compared to typical MM.[33] These patients presented with an 'immature' phenotype characterised by features such as lymphoplasmacytoid morphology and low CD138 expression. Importantly, several studies have demonstrated that the immature phenotype of MM is predominantly observed in the 1q WT group.[10,15,17] Indeed, among our 89

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TABLE 1 Patient characteristics ($N = 89$).

Parameters	*N* (%)
Age at diagnosis, year	
Median	76 (range: 30–97)
Sex	
F	43 (48)
Paraprotein type	
IgG	37 (42)
IgA	27 (30)
IgD	2 (2)
IgM	1 (1)
LCD	22 (25)
R-ISS at diagnosis	
I	10 (11)
II	48 (54)
III	31 (35)
R2-ISS at diagnosis	
I	7 (8)
II	13 (15)
III	49 (55)
IV	20 (22)
Serum LDH > ULN	20 (23)
Serum β2MG ≥ 3.5 mg/L	66 (74)
Cytogenetic abnormalities	
1q gain	20 (23)
1q amp	11 (12)
Isolated 1q gain/amp	17 (19)
t(4;14)	9 (10)
t(14;16)	2 (2)
del (17p)	12 (14)
t(11;14)	28 (31)
Immature phenotype MM	15 (17)

Abbreviations: F, female; ISS, international scoring system; LCD, light chain disease; LDH, lactate dehydrogenase; MM, multiple myeloma; ULN, upper limit of normal; β2MG, β2-microglobulin.

samples, 15 exhibited an immature phenotype and 14 did not coexist with 1q+. Thus, analyses were conducted taking into account the existence of low CD38 expression levels in the 1q WT group. To eliminate the impact of reduced CD38 expression due to immaturity, we excluded the immature MM phenotype from the 1q WT group. Our samples included a sample that had both 1q amp and an immature phenotype. To avoid overestimation, we classified this sample as part of the immature phenotype group. We then reassessed the CD38 expression in the 1q+ and 1q WT groups. Consequently, the CD38 levels were significantly lower in the 1q+ MM group (Figure 1B). This finding indicates that 1q+ MM demonstrated lower CD38 levels, regardless of their maturation stage. Furthermore, since the existence of 1q+ is associated with the existence of other high-risk chromosomal abnormalities,[10,15,17,38] we performed an analysis on isolated 1q+ MM. We found that the isolated 1q+ MM still exhibited significantly lower CD38 expression (Figure 1C). In addition, 1q amp MM was found to have a significantly lower CD38 expression than 1q gain MM (Figure 1D). As we previously reported, when we plotted these 89 primary samples of patients with MM by CD38/CD138 expression, we validated that the cases with the immature MM phenotype appeared predominantly in the $CD38^{low}/CD138^{low}$ population (Figure 1E). In contrast, 1q+ MM appeared most frequently in the $CD38^{low}/CD138^{high}$ fraction (72%), with their proportion being significantly higher than that in other fractions (Figure 1E,F). Moreover, age, sex, paraprotein type, R-international scoring system (ISS), R2-ISS and serum lactate dehydrogenase or β2-microglobulin levels did not correlate with CD38 expression. Collectively, these findings imply that 1q+ MM exhibits lower CD38 expression through a mechanism distinct from that at the maturation stage.

IL6R is overexpressed as the copy number of 1q increases

We observed that CD38 expression was reduced in patients with 1q+ MM. However, the reason for reduced CD38 expression in 1q+ MM remains unclear. To this end, we focused on two aspects. A previous report indicated that IL-6 downregulates CD38 expression via the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway in MM.[39] Another point was that *IL6R* is located on chromosome 1q21 region (Figure 2A).[22] Therefore, we examined the IL6R expression levels in our primary samples. As expected, our results demonstrated that as the copy number of 1q increased, IL6R expression increased (Figure 2B). This finding was consistent with the results obtained using a public dataset (Figure 2C).[40] Furthermore, we found a significant negative correlation between IL6R and CD38 levels in primary samples (Figure S1). This correlation was particularly strong when the samples with immature phenotypes were excluded (Figure 2D). These results suggested a close association between 1q+ MM, IL6R and CD38 expression.

CD38 downregulation in MM cells depends on the high levels of IL6R expression

Since we confirmed that IL6R expression was upregulated in 1q+ MM, we hypothesised that CD38 was downregulated in 1q+ MM due to IL6R overexpression and subsequent JAK/STAT pathway overactivation. To test this hypothesis, we prepared three HMCLs with 1q+ (H929, MOLP8 and MM.1S) and three HMCLs with 1q WT (SKMM2, KMS12BM and NCU-MM1). H929, MOLP8 and MM.1S exhibited 5, 4 and 3 copies of 1q respectively. We first examined the surface IL6R expression level among them, and consistent with our results from primary samples and public datasets, we observed a tendency for IL6R expression to increase with a higher copy number of

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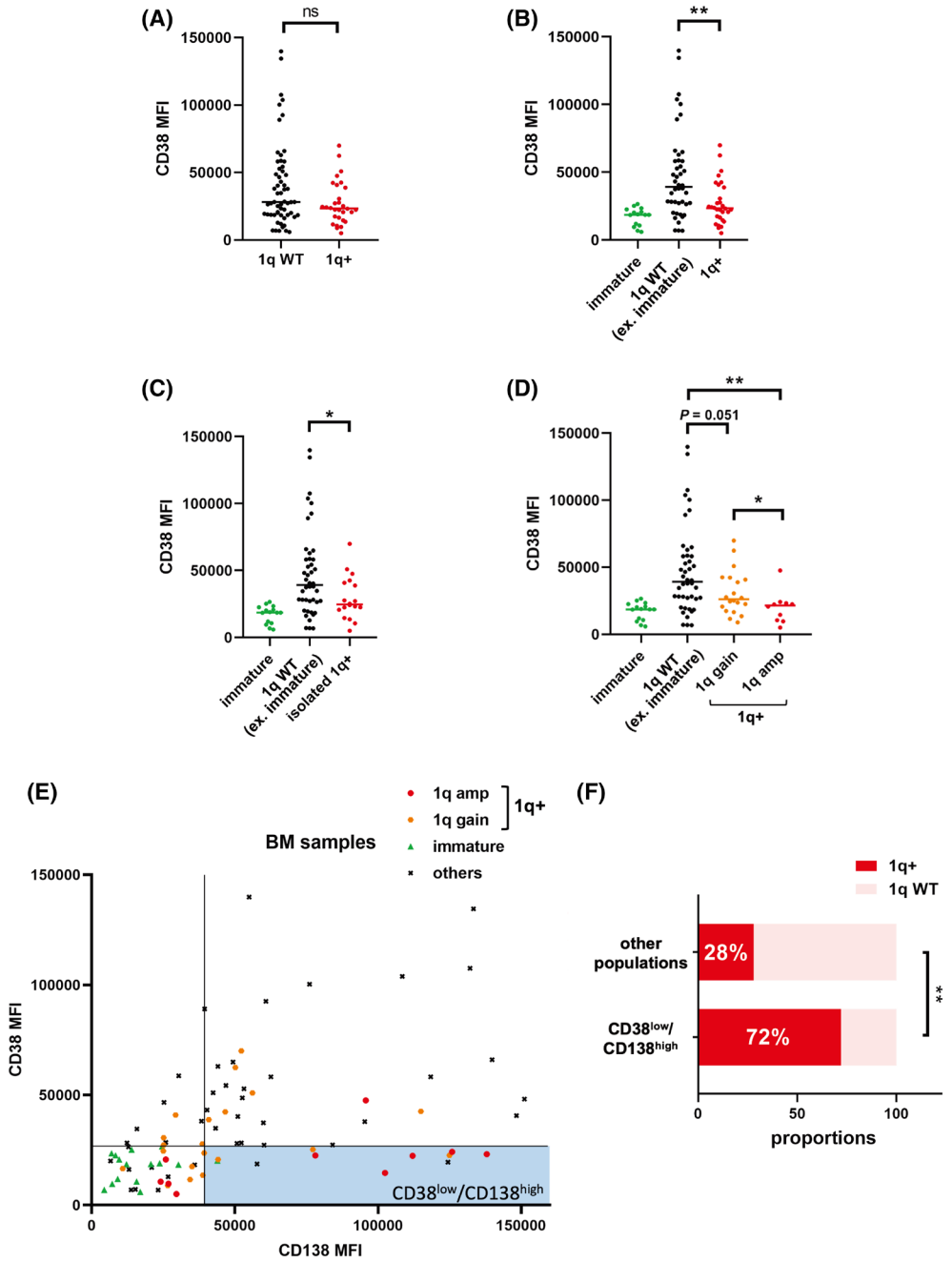

FIGURE 1 CD38 expression is reduced in patients with 1q+ MM. The bars indicate the median values of CD38 or CD138 MFI. The significance of the differences between the indicated groups was assessed using the Mann–Whitney *U* test, Kruskal–Wallis test and Fisher's exact test. (A) Comparison of CD38 MFI in 89 patients with newly diagnosed multiple myeloma with ($N = 30$) or without 1q+ ($N = 59$). CD38 MFI was assessed in the neoplastic plasma cell population (CD38+/CD138+/CD56+ or CD56−/CD19−), as previously described.[8,32] (B) Comparison of CD38 MFI between 1q+ MM group ($N = 30$), 1q WT group ($N = 44$) and the immature phenotype group ($N = 15$). (C) Comparison of CD38 expression among the isolated 1q+ MM group ($N = 17$), 1q WT group ($N = 44$), and the immature phenotype group ($N = 15$). (D) Comparison of CD38 expression among 1q amp MM ($N = 10$), 1q gain MM ($N = 20$), 1q WT MM ($N = 44$) and the immature phenotype ($N = 15$) groups. (E) CD38 and CD138 MFI in 89 primary samples including 1q amp MM ($N = 10$), 1q gain MM ($N = 20$), 1q WT MM ($N = 44$) and the immature phenotype ($N = 15$) groups. In this plot, the thin horizontal line indicates the median value of CD38 and the vertical line represents that of CD138. (F) Proportions of patients with 1q+ MM in the $CD38^{low}/CD138^{high}$ and other populations. $*0.01 \leq p < 0.05$; $**0.001 \leq p < 0.01$. 1q amp, 1q amplification; 1q WT, 1q wild type; 1q+, positive for chromosome 1q gain/amplification; MFI, mean fluorescence intensity; MM, multiple myeloma; ns, not significant.

1q, as assessed by FCM (Figure 3A) and quantitative reverse transcription polymerase chain reaction (RT-PCR) (Figure S2A). In contrast, almost no IL6R expression was observed in the NCU-MM1 (Figure 3A). Furthermore, there appeared to be no correlation between the expression levels of IL6ST and the copy number of 1q (Figure S2B). We then treated these six HMCLs with IL-6 at a concentration of 10 ng/mL and incubated them for 3 days, based

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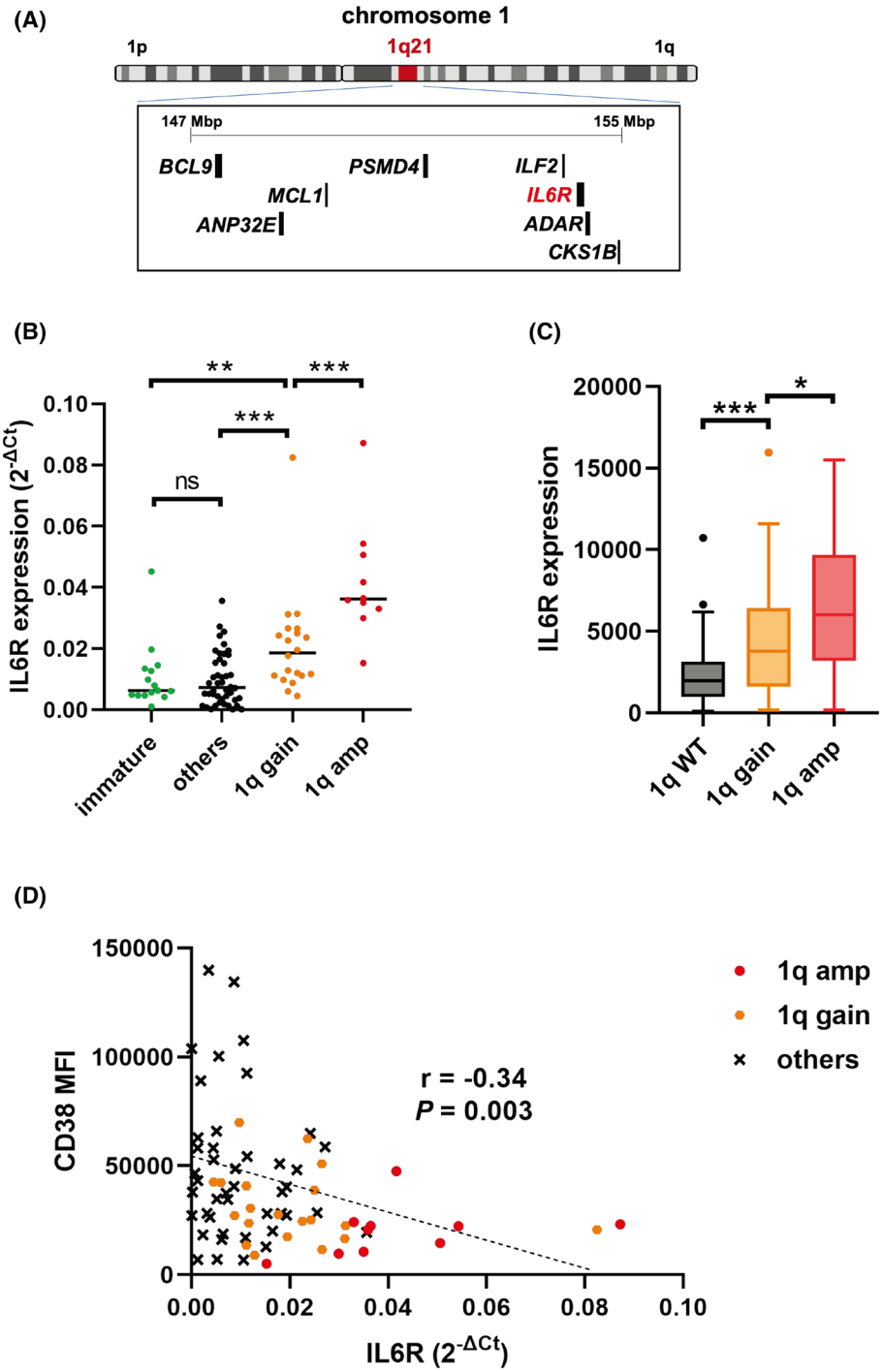

FIGURE 2 IL6R is overexpressed as the copy number of 1q increases. The bars indicate median values of IL6R expression with interquartile ranges. The significance of differences between the indicated groups was assessed using the Kruskal–Wallis test. Correlations were assessed using the Spearman test. (A) The figure illustrating chromosome 1 and an enlarged view of the 1q21 region. Candidate driver genes and their locations are also described. (B) Comparison of IL6R MFI among primary samples and (C) in the Arkansas dataset (GSE4581) according to 1q status. In the Arkansas dataset, a total of 414 samples were available. Among these, the 1q copy number was unknown for 228 samples. The remaining 186 samples were analysed (38 with 1q amp, 55 with 1q gain and 93 with 1q WT). (D) Correlation between IL6R and CD38 expression in primary samples excluding those with an immature phenotype. *$0.01 \leq p < 0.05$; **$0.001 \leq p < 0.01$; ***$p < 0.001$. 1q WT, chromosome 1q wild type; IL6R, interleukin 6 receptor; MFI, mean fluorescence intensity; MM, multiple myeloma; ns, not significant; *r*, correlation coefficient.

on previous reports.[24,41] The median IL-6 concentration in the BM of patients with MM has been reported to be 20 ng/mL.[41] We confirmed that 1q+ HMCLs showed reduced CD38 expression (Figure 3B,C) upon IL-6 treatment. Moreover, CD38 expression in the HMCLs with 1q amp, such as H929 and MOLP8, was likely to be downregulated compared to that in MM.1S. Interestingly, CD38 expression was also downregulated in KMS12BM, which has 1q

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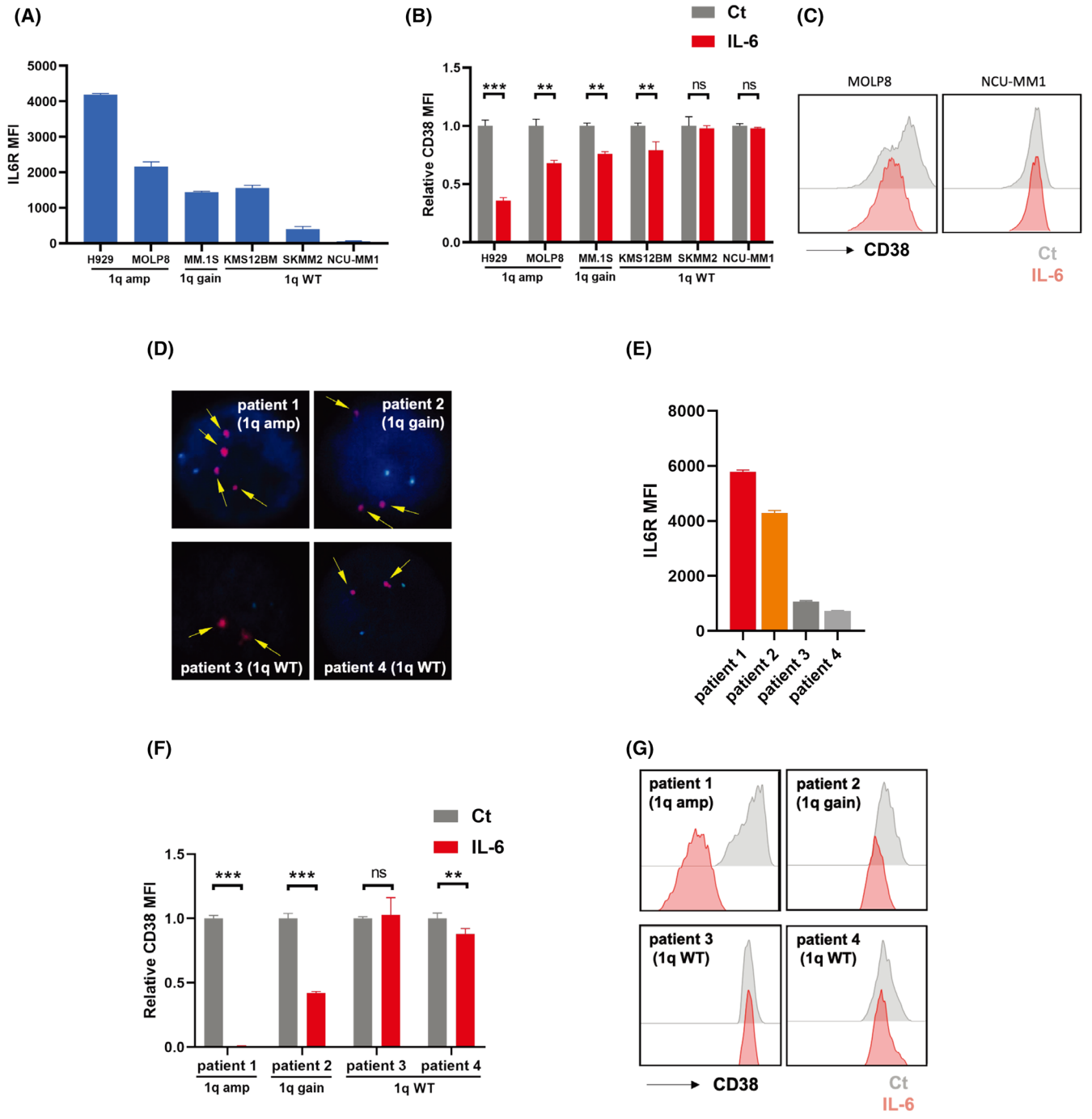

FIGURE 3 CD38 downregulation in MM cells depends on the high levels of IL6R expression. The bars indicate the mean ± 95% confidence interval of three independent experiments. The significance of differences between the indicated groups was assessed using the Student's *t*-test. (A) IL6R expression and copy status of 1q in HMCLs. H929 has five copies of 1q and MOLP8 has four copies. (B) CD38 expression levels before and after IL-6 administration in six HMCLs. (C) Representative histograms of CD38 expression in HMCLs. (D) FISH analytical results using the CKS1B probe indicated by yellow arrows. (E) IL6R expression levels. (F) CD38 expression levels before and after administration of IL-6. (G) Histograms of CD38 expression in the four primary samples. $^{**}0.001 \leq p < 0.01$; $^{***}p < 0.001$. CKS1B, CDC28 protein kinase regulatory subunit 1B; FISH, fluorescence in situ hybridisation; HMCLs, human myeloma cell lines; IL6R, interleukin 6 receptor; ns, not significant; *r*, correlation coefficient.

WT, but a high level of surface IL6R expression comparable to that in MM.1S. On the other hand, other HMCLs with 1q WT, showing lower IL6R expression, did not show significant CD38 downregulation when treated with IL-6. In our primary samples, we administered IL-6 and incubated them for 2 days, followed by CD38 expression analysis using multicolour FCM (Materials and Methods; Figure S3). We found that IL6R expression was significantly higher in samples with 1q gain or amp than in those with 1q WT (Figure 3D,E). Importantly, CD38 expression was markedly downregulated in samples with 1q gain or amp compared with those with 1q WT (Figure 3F,G).

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These results demonstrated that IL-6 downregulates CD38 expression owing to the overexpression of surface IL6R in patients with 1q+ MM.

JAK/STAT pathway overactivation by the treatment with IL-6 is mainly shown in 1q+ HMCL and NDMM

Next, we examined the status of the JAK/STAT pathway in each HMCL after IL-6 administration. We confirmed that IL-6 resulted in robust upregulation of p-STAT3 in HMCLs with 1q amp, whereas p-STAT3 was not upregulated even when treated with IL-6 in NCU-MM1 (Figure 4A). Furthermore, 1q+ HMCLs exhibited an enhanced proliferative capacity upon IL-6 treatment (Figure 4B), as previously reported.[24] Conversely, IL-6 administration did not significantly enhance the proliferation of HMCLs with 1q WT (Figure 4B). This observation further suggests that the IL-6/JAK/STAT pathway is activated in 1q+ HMCLs. In addition, IL6R and STAT3 mRNA levels were positively correlated in our primary samples and in the aforementioned public dataset (Figure 4C,D). Moreover, after reanalysing the RNA sequence data from patients with MM in the CoMMpass study, IL-6/STAT signalling ranked third among the pathways significantly enriched in 1q+ NDMM (Figure 4E). These findings demonstrate that the JAK/STAT pathway is indeed overactivated by treatment with IL-6, resulting in a CD38 reduction in the 1q+ population.

Ruxolitinib (Ruxo) and tocilizumab (Toci) restore the CD38 expression levels that had been reduced due to IL-6

A previous study showed that several samples from patients with MM showed CD38 restoration after treatment with the JAK1/2 inhibitor Ruxo.[39] However, experimental results indicated that CD38 expression was not restored in all patient samples. Based on the results of previous experiments, we hypothesised that the restoration of CD38 expression by Ruxo treatment occurs specifically in 1q+ MM, as the JAK/STAT pathway is upregulated in 1q+ MM. To test our hypothesis, we treated HMCLs with Ruxo, Toci, an anti-IL6R monoclonal antibody and IL-6, and incubated them for 3 days. We confirmed that Ruxo and Toci administration effectively restored CD38 from the suppression induced by IL-6, elevating its levels to approximately the control levels or even higher specifically in 1q+ HMCLs and KMS12BM (Figure 5A,B). In contrast, other HMCLs with 1q WT did not show this phenomenon when treated with Ruxo or Toci (Figure 5A,B). Interestingly, this effect was also observed in primary samples after treatment with Ruxo or Toci (Figure 5C). Furthermore, in MOLP8, ADCC induced by Dara was impaired by the addition of IL-6 but was restored by Toci treatments (Figure 5D). Notably, despite the restoration of CD38 by Ruxo (Figure 5A), ADCC was not restored. These results suggest that targeting the JAK/STAT pathway, particularly using Toci, may be useful for the treatment of 1q+ MM.

DISCUSSION

In this study, we revealed that CD38 expression was significantly reduced in the 1q+ MM group, especially in 1q amp MM. We also confirmed the high expression of IL6R in 1q+ MM, as the *IL6R* gene is located at 1q21. This IL6R enrichment in 1q+ MM induces robust upregulation of p-STAT3 and activation of the JAK/STAT pathway, leading to a significant reduction in CD38 in 1q+ MM when treated with IL-6. This finding may be a significant reason for the reduced efficacy of Dara in patients with 1q+ MM because CDC, which is one of the potencies of Dara,[5,6] depends on the amount of CD38 expressed in myeloma cells.

CD38 expression is well known to be regulated by various complex mechanisms beyond the 1q+ status,[42] including JAK/STAT pathway activation,[39] retinoic acid signals,[43] deacetylation or demethylation of the CD38 promoter[44,45] and loss of KDM6A.[46] Our experimental results, including the relatively high CD38 levels observed in MOLP8 cells in the absence of IL-6 (Table S1), further suggest that 1q+ status alone cannot fully account for CD38 expression. Among our 89 MM primary samples, several 1q+ MM samples still exhibited relatively high CD38 expression even though they were all exposed to IL-6 in the patient's BM (Figure 1E). This might be due to IL-6 concentrations in the BM microenvironment below the median level of 20 ng/mL and/or the influence of those CD38-regulating mechanisms. Nonetheless, the overall findings from our 89 MM primary samples suggest that 1q+ MM exhibits significantly lower CD38 expression than 1q WT MM, even in the clinical setting, indicating that 1q+ is one of the key factors in CD38 regulation.

As mentioned earlier, Dara not only eradicates tumour cells through its cytotoxic activity[5,6] but also activates tumour immunity mediated by T cells.[7,8] However, 1q+ MM may also suppress the 'immunomodulatory effects' of Dara because the immunomodulatory effect likely depends on the tumour burden. Indeed, tumour debulking can lead to improved outcomes with subsequent immunotherapy. This improvement is attributed to several factors, including the release of tumour antigens that stimulate the immune system, a reduction in immunosuppressive cytokines released by the tumour due to decreased tumour burden and a decrease in treatment-resistant clones due to clonal heterogeneity.[47,48] In actual cases such as ovarian cancer and non-small cell lung cancer, the overall survival can be prolonged by performing molecular targeted therapy or programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors after tumour debulking surgery.[49,50] An increase in the effector T cell/ tumour ratio also leads to an enhanced anti-tumour effect[51] even under Dara administration.[52] These findings suggest that appropriate tumour debulking significantly influences the efficacy of immunotherapy.

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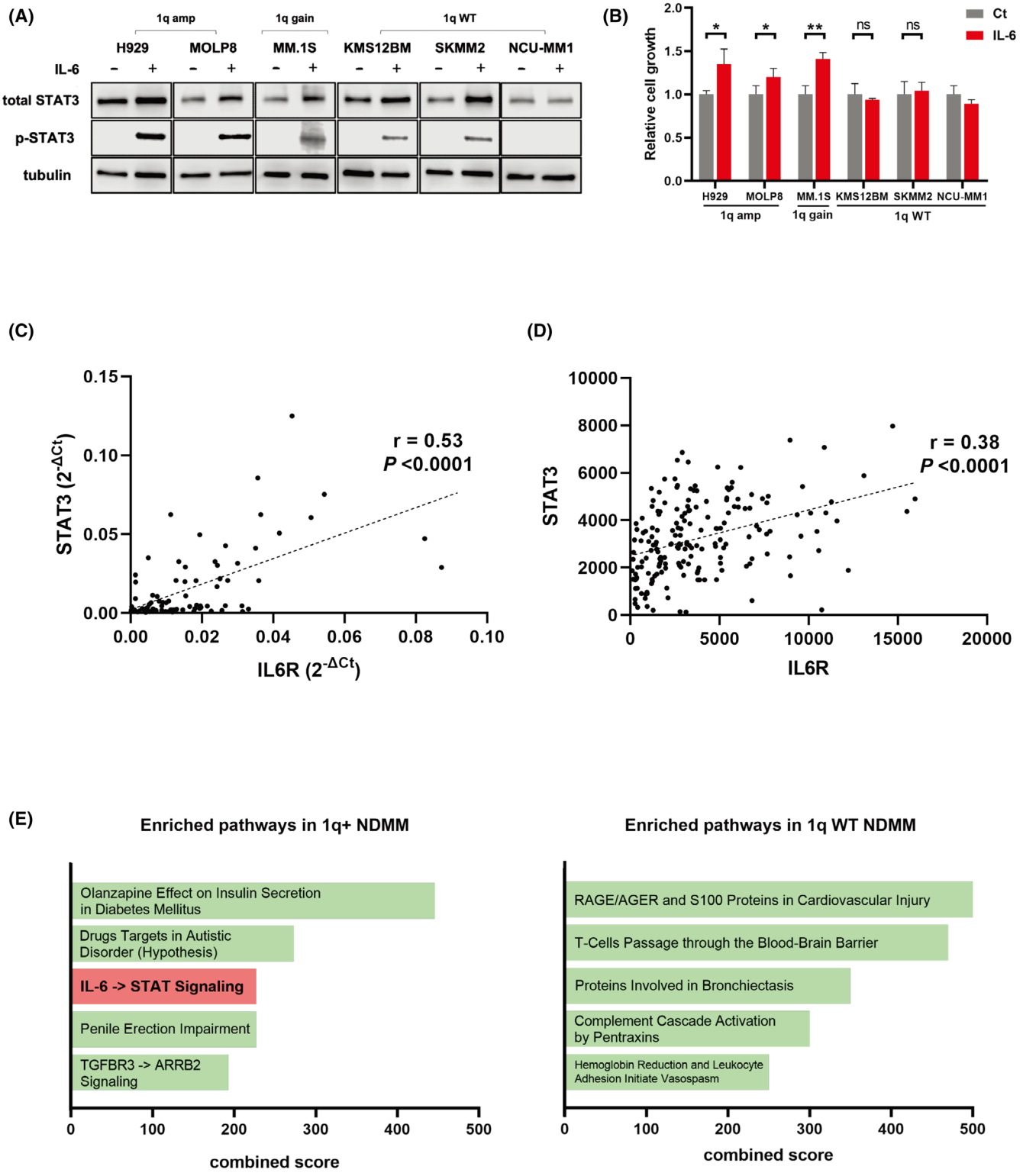

It is also important to determine whether the 1q+ populations are the major or minor clones in that particular case. As reported by Hanamura et al., the likelihood that more than 80% of all tumour cells express 1q+ was 91% in 1q amp NDMM and 54% in 1q gain NDMM.[10] Thus, not only was the CD38 expression level in 1q amp MM cells reduced, but the proportion of such cells within the total tumour cell population was also higher in 1q amp MM. Our results and those from previous reports suggest that appropriate tumour debulking is not achieved in 1q amp MM, which may result in the insufficient immunomodulatory effects of Dara and a shorter PFS. Thus, it is worth exploring whether quadruplet therapies, such as Dara, bortezomib, lenalidomide and dexamethasone (Dara-VRd), may improve the prognosis by achieving sufficient debulking with the addition of proteasome inhibitors in patients with MM with 1q amp.[53]

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FIGURE 4 JAK/STAT pathway overactivation by the treatment with IL-6 is mainly shown in 1q+ HMCL and NDMM. The bars indicate the mean ± 95% confidence interval of three independent experiments. The significance of differences between the indicated groups was assessed using the Student's *t*-test. Correlations were assessed using the Spearman test. (A) Western blotting analysis of total STAT3 and p-STAT3 levels after treatment with IL-6. Tubulin was used as a control. (B) The proliferative capacity of six HMCLs treated with IL-6. (C) Correlation between IL6R and STAT3 mRNA expression levels in our 89 primary samples. Expression levels were normalised to GAPDH, and the relative expression levels of specific mRNA were presented as $2^{-\Delta Ct}$. (D) Correlation between IL6R and STAT3 levels in the Arkansas dataset (GSE4581) ($N = 186$). (E) Pathway analysis by reanalysing RNA-seq data from patients in the CoMMpass study using Enrichr. The left figure represents data from the 1q+ MM group, while the right figure represents data from the 1q WT MM group. The data were derived from supplemental data shown in the paper reported by Boyle et al. Combined score was computed by multiplying the two scores as follows: (combined score = −log (*P*) × odds ratio). *p*-value was computed using the Fisher's exact test. The odds ratio was calculated using a 2 × 2 contingency table. *$0.01 \leq p < 0.05$; **$0.001 \leq p < 0.01$. GAPDH, glyceraldehyde 3-phosphate dehydrogenase; HMCL, human myeloma cell line; IL-6, interleukin-6; IL6R, interleukin-6 receptor; JAK, Janus kinase; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; ns, not significant; *r*, correlation coefficient; RNA-seq, ribonucleic acid sequencing; STAT3, signal transducer and activator of transcription 3; WT, wild type.

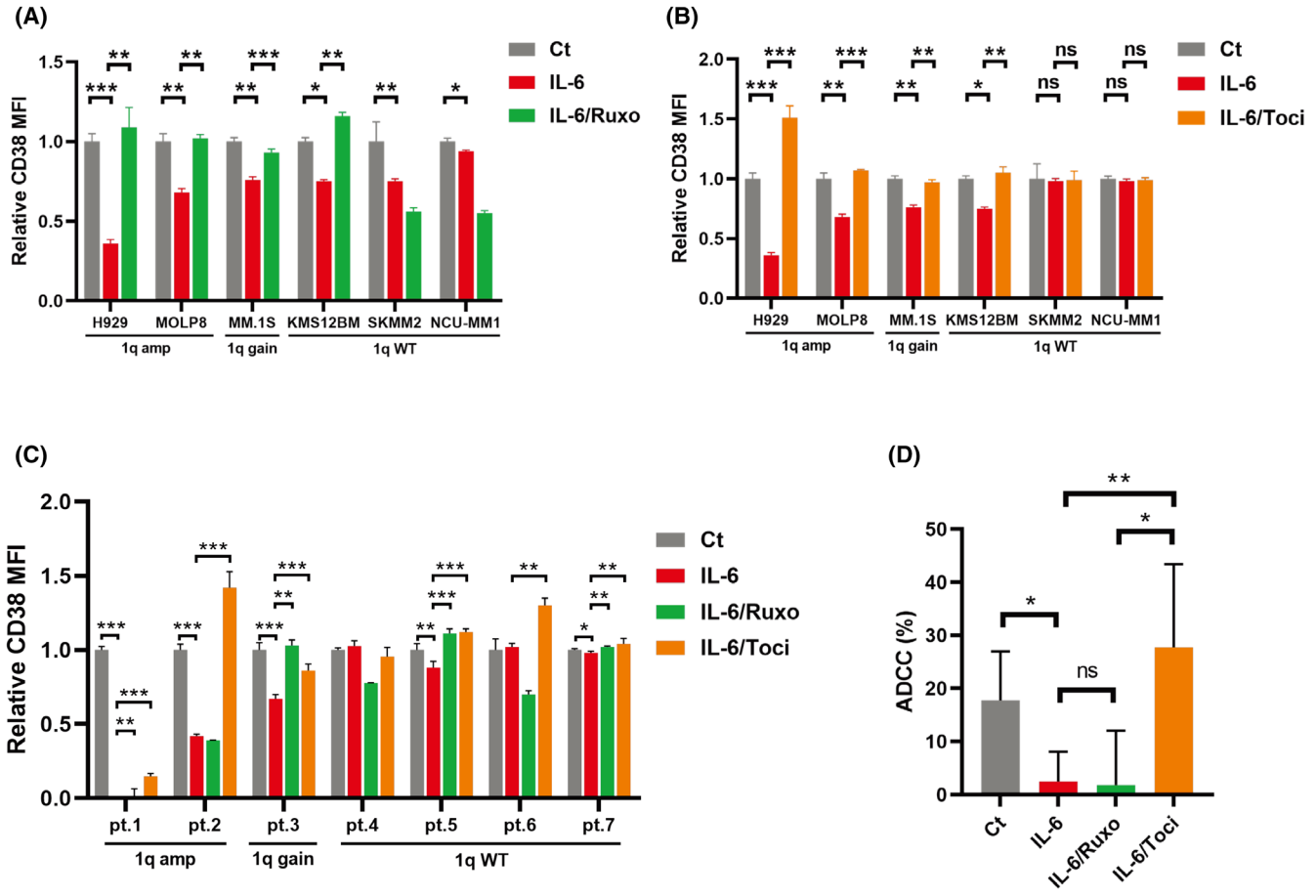

FIGURE 5 Toci restores the CD38 expression levels and ADCC activity that had been reduced due to IL-6 treatment. The bars indicate the mean ± 95% confidence interval of three independent experiments. The significance of differences between the indicated groups was assessed using the Student's *t*-test. (A) CD38 expression levels before and after the administration of Ruxo and (B) Toci in HMCLs. (C) CD38 expression in six primary MM samples. (D) ADCC activity of daratumumab in MOLP8 cells. *$0.01 \leq p < 0.05$; **$0.001 \leq p < 0.01$; ***$p < 0.001$. ADCC, antibody-dependent cellular cytotoxicity; HMCLs, human myeloma cell lines; IL-6, interleukin-6; MM, multiple myeloma; ns, not significant; *r*, correlation coefficient; Ruxo, ruxolitinib; Toci, tocilizumab.

Although one of the limitations of the current study is that we did not analyse the sensitivity of Dara to tumour cells, our studies on CD38 reduction suggest that the mechanisms underlying CD38 reduction might vary among each chromosomal abnormality of MM. In approximately half of the cases of t(11;14) MM, CD38 reduction was observed due to the immature phenotype,[33] whereas in 1q+ MM, CD38 reduction was caused by overactivation of the JAK/STAT pathway. Given that anti-CD38 antibodies are now considered the gold standard for MM treatment, understanding the mechanisms underlying CD38 reduction and developing individualised treatment strategies may be necessary. Clinical trials are currently being conducted to assess the efficacy of Ruxo plus steroids in treating MM.[54] It might

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be essential to analyse its effects specifically in patients with 1q+ MM, especially if the combination of anti-CD38 antibodies and Ruxo is tested in future studies. Notably, although Ruxo restored CD38 expression, Dara-induced ADCC did not recover. This suggests that the impairment of ADCC may be more strongly influenced by dysfunction of NK cells, for which the development, activation and cytotoxic activity are dependent on STAT3[55] rather than restoration of CD38 on tumour cells by Ruxo. Therefore, the combination of Toci may be more effective than Ruxo in efficiently eliminating tumour cells in 1q+ MM. Importantly, the all-trans retinoic acid (ATRA)-induced increase in CD38 expression did not improve the efficacy of Dara. This absence of benefit is attributed to the transient nature of CD38 upregulation,[56] highlighting the need for further studies to investigate combination therapies with agents that achieve sustained CD38 upregulation to potentially enhance Dara's therapeutic potential.

In conclusion, IL6R overexpression due to 1q+ and subsequent robust JAK/STAT pathway stimulation reduced CD38 expression. Our findings support the importance of precision therapy in CD38-targeted treatments for MM, which can potentially contribute to the development of future treatment strategies.

AUTHOR CONTRIBUTIONS

W.K. collected, analysed the data and wrote the manuscript. A.K. designed the study and prepared the manuscript. M.Y., S.I. and Y.T. provided technical assistance. T.K., S.I., K.N. and K.M. supported this study and provided BM samples. N.T. supervised the study.

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CONFLICT OF INTEREST STATEMENT

A.K. received remuneration for lectures from Janssen Pharmaceutical, Bristol Myers Squibb and Sanofi. S.I. received remuneration for lectures from Janssen Pharmaceutical. N.T. received remuneration for lectures from Novartis Pharma, Otsuka Pharmaceutical and Pfizer, Inc. N.T. received trust/joint research funds from Novartis Pharma, Otsuka Pharmaceutical, Pfizer Inc. and Astellas Pharma. N.T. received scholarship funds from Astellas Pharma, Otsuka Pharmaceutical, Asahi Kasei Corporation and Mochida Pharmaceutical Co., Ltd. The authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available upon request from the corresponding author. The data are not publicly available because of privacy and ethical restrictions.

ETHICS APPROVAL STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards of Kameda Medical Center (protocol number: 19-014) and Akita University Hospital (3140).

PATIENT CONSENT STATEMENT

Written informed consent was obtained from all the patients.

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