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LETTER

sMAdCAM-1 is decreased after allo-HCT, along with gut microbiota dysbiosis, and is associated with hematopoietic recovery

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Chemotherapy and total-body irradiation-based conditioning regimens, together with the use of broad-spectrum antibiotics during allogeneic hematopoietic cell transplantation (allo-HCT), induce gut microbiota dysbiosis,[1,2] which is associated with poor patient outcomes.[1] Furthermore, it has been reported that the intestinal microbiome and the hematopoietic system interplay.[3,4]

Fidelle et al. showed recently in a cohort of non-small cell lung cancer patients that antibiotic-induced dysbiosis led to the loss of MAdCAM-1 tissular expression and decreased soluble MadCAM-1 (sMAdCAM-1).[5] MAdCAM-1, expressed on endothelial cells, interacts with the α4β7 integrin to direct hematopoietic stem cell (HSC) homing and engraftment[6] and the trafficking of lymphocytes into Peyer's patches and the intestinal lamina propria.[7] It is established that the MAdCAM-1/α4β7 axis is implicated in the recruitment of effector donor CD8 T cells to the recipient intestine and that blocking this axis prevents graft-versus-host disease (GvHD).[8,9] Altogether, this suggests that the interplay between the MAdCAM-1/α4β7 axis, the microbiota, and the use of antibiotics warrants investigation in the setting of allo-HCT. We, therefore, aimed to investigate the impact of sMAdCAM-1 level on patients' outcomes after allo-HCT, particularly GvHD and hematopoietic recovery.

This retrospective study comprised a cohort of 279 consecutive adult patients with a hematological malignancy who underwent allo-HCT between October 2012 and June 2018. Patient and disease characteristics are detailed in Table 1. Written informed consent was obtained from each patient in accordance with the principles of the Declaration of Helsinki. Sera were collected prior to allo-HCT (baseline timepoint), the day of allo-HCT (D0), and at D20, 90, and 360 after allo-HCT, and sMAdCAM-1 was quantified using the Human MAdCAM-1 DuoSet ELISA kit (Bio-Techne/R&D Systems). Patients' supportive care (including infection prophylaxis), serum preparation and sMAdCAM-1 quantification, stool collection, DNA extraction and 16S sequencing, and analysis and statistical methods are listed in the Supporting Information File.

Because tissue biopsies are difficult to obtain and sMAdCAM-1 originates from cleavage of tissular MAdCAM-1, we evaluated sMAdCAM-1 concentrations in the blood using ELISA as a surrogate marker for tissular MadCAM-1 expression. sMAdCAM-1 levels significantly decreased following conditioning, reaching 4234 pg/mL at D0 versus 8815 pg/mL at baseline ($p < 0.0001$), and continued to decline to 3277 pg/mL by D20 ($p < 0.0001$). At D90 ($n = 221$), while sMAdCAM-1 levels increased compared to D20, being 4275 pg/mL ($p < 0.0001$), it remained significantly lower compared to baseline samples ($p < 0.0001$, Figure 1A). Patient age, gender, and underlying malignancies (myeloid vs. lymphoid) did not impact sMAdCAM-1 concentrations at baseline (Supporting Information S1: Figure 1A–C).

We observed a statistically significant correlation between bacterial diversity and sMAdCAM-1 ($p = 0.006$, $R^2 = 0.091$ Figure 1B). Interestingly, patients with greater bacterial diversity (Shannon index cutoff = 4) had significantly higher sMAdCAM-1 levels compared to

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TABLE 1 Patient and transplant characteristics.

All patients (n = 279)	
Patient age in years, median (range)	56 (16–76)
Gender (%)	
Male	169 (60.6%)
Female	110 (39.4%)
Disease (%)	
Myeloid	194 (69.5%)
Acute myeloid leukemia	123 (63.4%)
Myeloproliferative neoplasms	47 (24.2%)
Myelodysplastic syndromes	24 (12.4%)
Lymphoid	85 (30.6%)
Chronic lymphocytic leukemia	1 (1.2%)
Hodgkin lymphomas	11 (12.9%)
Multiple myeloma	7 (8.2%)
Non-Hodgkin lymphomas	23 (27.1%)
Acute lymphoid leukemia	43 (50.6%)
DRI (%)	
Low	3 (1.1%)
Intermediate	175 (62.7%)
High	91 (32.6%)
Very high	10 (3.6%)
Graft source (%)	
Bone marrow	22 (7.9%)
Peripheral blood stem cells	257 (92.1%)
Regimen intensity (%)	
RIC	74 (26.5%)
RTC	122 (43.7%)
Sequential	83 (29.7%)
Donor type (%)	
Haploidentical donor	93 (33.3%)
Matched sibling donor	77 (27.6%)
Matched unrelated donor	109 (39.1%)
GvHD prophylaxis (%)	
CsA	38 (13.6%)
CsA-MMF	226 (81.0%)
CsA-MTX	15 (5.4%)
PTCy (%)	
Yes	106 (38.0%)
No	173 (62.0%)
ATG (%)	
Median dose (range)	5 mg/kg (2–12.5)
No	21 (7.5%)
Yes	258 (92.5%)
PIM exposure before Day 0 (%)	
Yes	79 (28.3%)
No	200 (71.7%)
PIM exposure from the start of conditioning to neutrophil engraftment (%)	
Yes	231 (82.8%)
No	48 (17.2%)

Abbreviations: aGvHD, acute GvHD; ATG, antithymocyte globulin; cGvHD, chronic GvHD; CsA, cyclosporin A; DRI, disease risk index; GvHD, graft-versus-host disease; MMF, mycophenolate mofetil; MTX, methotrexate; PIM, piperacillin-tazobactam, imipenem-cilastatin or meropenem; PTCy, post-transplant cyclophosphamide; RIC, reduced intensity conditioning; RTC, reduced toxicity conditioning.

patients with lower bacterial diversity (median, 6288 vs. 4488 pg/mL, $p = 0.0041$, Figure 1C). Importantly, we previously reported, using the same data set, that patients with a higher Shannon index had a better outcome, in particular a better disease-free survival.[10] We then assessed the impact of antibiotic exposure on sMAdCAM-1 levels, focusing on antibiotics with a broad anti-anaerobic spectrum, piperacillin-tazobactam, imipenem-cilastatin, or meropenem (PIM). Patients who received PIM during conditioning (before D0) had significantly lower sMAdCAM-1 concentrations at D0 (median, 3056 vs. 4747 pg/mL, $p < 0.0001$, Figure 1D). In contrast, the use of PIM during the conditioning regimen and neutropenic phase after allo-HCT had no impact on sMAdCAM-1 concentrations at D20 (Figure 1E), probably owing to the small number of patients ($n = 48/279$, 17%) that did not receive PIM.

Subsequently, we evaluated the impact of sMAdCAM-1 on patients' outcomes. Median follow-up among surviving patients was 58 months (range, 4–93). First, we analyzed the impact of sMAdCAM-1 on the cumulative incidence (CI) of grade II–IV and III–IV acute GvHD (aGvHD) and did not observe any statistically significant differences between patients with low versus high sMAdCAM-1 at D0 or D20 after allo-HCT (Supporting Information S1: Figure 2A–D). Of note, there were also no differences in the CI of overall and stage 2–4 gastrointestinal aGvHD between patients with low versus high sMAdCAM-1 at D0 ($p = 0.97$ and $p = 0.70$, respectively, data not shown). One explanation for this absence of difference may be that while high MAdCAM-1 expression, particularly by the ileal venule in the crypt base,[11] leads to alloreactive donor T cell infiltration and an increased risk of aGvHD, MAdCAM-1 is downregulated by the use of broad-spectrum antibiotics,[5] which are also associated with increased GvHD mortality.[12] Assessment of MAdCAM-1 expression on gut biopsies in those patients may have shed some light on our findings, but unfortunately, no samples were available to perform such experiments.

Considering the role of the MAdCAM-1 and α4β7 integrin in the migration of hematopoietic progenitors and mature effector cells in the periphery,[6] we then investigated the relationship between sMAdCAM-1 concentrations and hematopoietic recovery. We found that neutrophil recovery was significantly longer in patients with low sMAdCAM-1 concentrations at D20, being 17 days (range, 8–53 days), versus 15 days (range, 5–29 days) in those with high sMAdCAM-1 concentrations at D20 ($p < 0.0001$, Supporting Information S1: Figure 3A). Similarly, platelet recovery $>20 \times 10^9$/L was significantly longer in patients with low versus high sMAdCAM-1 concentrations at D20, being 12 days (range, 0–78 days) versus 10 days (range, 0–35 days), respectively ($p = 0.002$, Supporting Information S1: Figure 3B). The D28 CI of neutrophil recovery (absolute neutrophil count [ANC] $> 0.5 \times 10^9$/L) was lower in patients with lower sMAdCAM-1 concentrations at D0 and D20, being 90.8% and 96.7%, respectively, versus 96.1% and 99.2% in patients with higher sMAdCAM-1

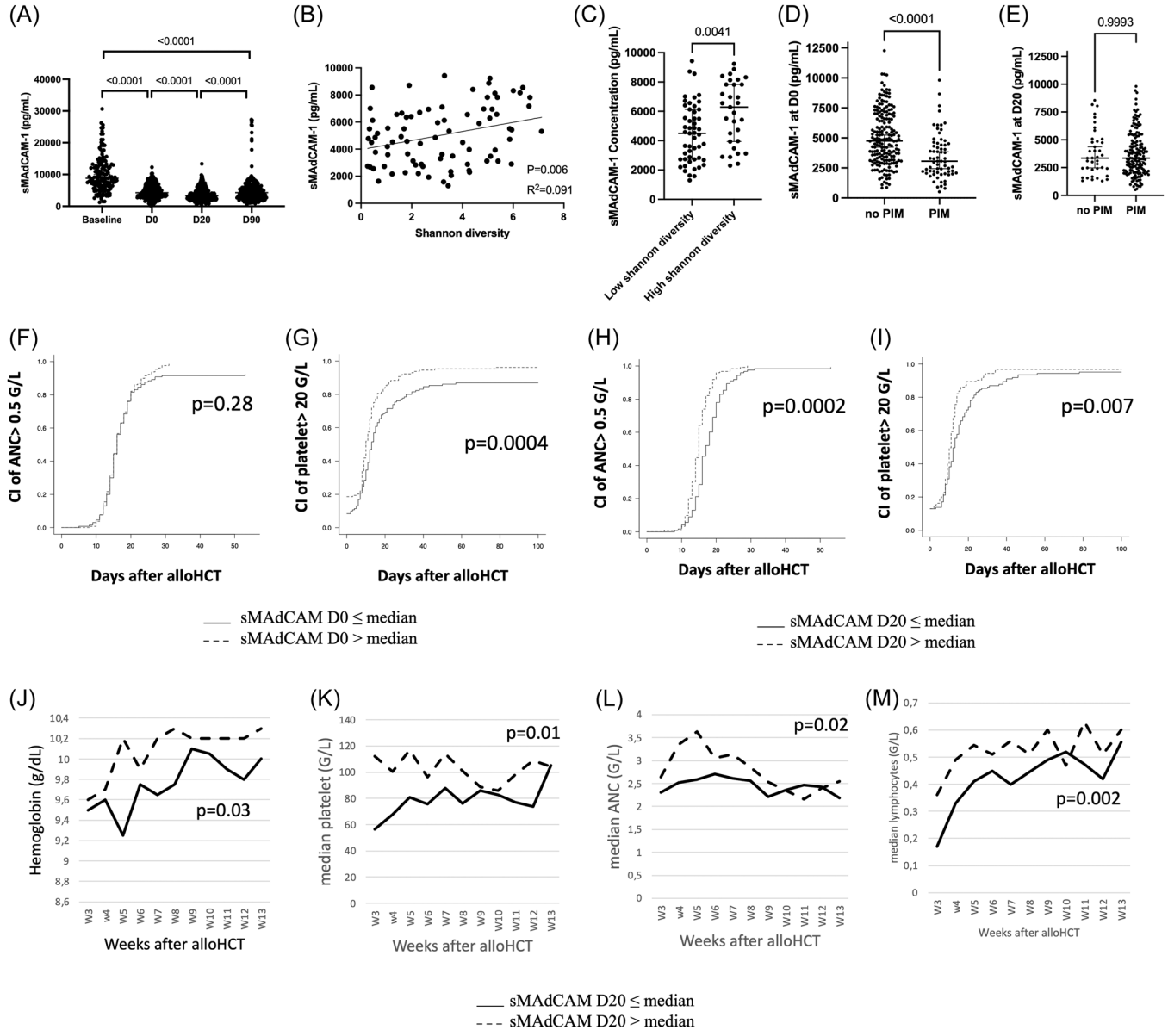

FIGURE 1 **Interplay between sMAdCAM-1 levels, gut microbiota diversity, antibiotic exposure, and hematopoietic recovery after allo-HCT.** **(A)** Dynamics of sMAdCAM-1 concentrations at baseline ($n = 144$), Day 0 ($n = 259$), Day 20 ($n = 246$), and Day 90 ($n = 221$) post-allo-HCT. **(B)** Correlation between sMAdCAM-1 concentrations at Day 0 and 20 and microbiota diversity represented by the Shannon index (Pearson correlation, $n = 82$, $r = 0.29$, $p = 0.006$). **(C)** sMAdCAM-1 concentrations in patients with low ($n = 51$) versus high Shannon diversity ($n = 31$) ($p = 0.0041$). **(D)** sMAdCAM-1 concentrations at Day 0 in patients exposed ($n = 72$) versus unexposed ($n = 187$) to anaerobic antibiotics (PIM) ($p < 0.0001$). **(E)** sMAdCAM-1 concentrations at Day 20 in patients exposed to anaerobic antibiotics PIM ($n = 206$) versus unexposed to anaerobic antibiotics (PIM) ($n = 40$) ($p = 0.9993$). Each dot represents a single patient; error bars represent median with interquartile range. **(F–G)** Cumulative incidence of absolute neutrophil recovery >0.5 G/L) and platelet recovery >20 G/L according to sMAdCAM-1 levels at Day 0 (sMAdCAM D0 ≤ median or sMAdCAM D0 > median). **(H, I)** Cumulative incidence of absolute neutrophil recovery >0.5 G/L and platelet recovery >20 G/L according to sMAdCAM-1 levels at Day 20 (sMAdCAM D20 ≤ median or sMAdCAM D20 > median) ($p = 0.0002$ and $p = 0.007$, respectively). Weekly median absolute counts of **(J)** hemoglobin, **(K)** platelets, **(L)** neutrophils, and **(M)** lymphocytes in 246 allo-HCT patients according to sMAdCAM-1 levels. ($p = 0.03$, $p = 0.01$, $p = 0.02$, and $p = 0.002$, respectively). For cumulative incidence of neutrophil and platelet recovery, groups were compared using Gray's test. alloHCT, allogeneic hematopoietic cell transplantation; med, median.

concentrations ($p = 0.28$ and $p = 0.0002$, respectively, Figure 1F,H). Similarly, the D28 CIs of platelet recovery >20 × 10^9/L were significantly lower in patients with lower sMAdCAM-1 concentrations at D0 and D20, being 76.9% and 85.4%, respectively, versus 91.5% and 93.5%, respectively, in patients with higher sMAdCAM-1 concentrations ($p = 0.0004$ and $p = 0.0065$, respectively, Figure 1G,I).

Studies have highlighted the multifactorial nature of hematopoietic reconstitution. We performed a multivariate analysis that included key factors associated with hematopoietic recovery in addition to the use of PIM and sMAdCAM-1 level (Supporting Information S1: Table 1). High D20 sMAdCAM-1 levels were the stronger predictor of ANC > 0.5 G/L recovery (high vs. low, hazard ratio [HR], 1.80, 95% confidence interval [95% CI], 1.40–2.32, $p < 0.000\,01$). Similarly, sMAdCAM-1 levels at D0 were significantly associated with the CI of platelet recovery >20 × 10^9/L (high vs. low, HR = 1.56, 95% CI, 1.22–1.99, $p = 0.0004$) and >50 × 10^9/L (high vs. low, HR = 1.51, 95% CI, 1.15–1.98, $p = 0.0032$).

To further investigate the impact of sMAdCAM-1 levels at D20 on hematopoietic recovery after allo-HCT, we compared cell counts up to

D90 after allo-HCT. Overall, we observed higher counts of hemoglobin, platelets, neutrophils, and lymphocytes in patients with higher sMAdCAM-1 levels at D20 (Figure 1J–M, $p = 0.03$, $p = 0.01$, $p = 0.02$ and $p = 0.002$, respectively). In addition, we found that patients with low sMAdCAM-1 levels at D0 have significantly more graft failure, 9.2%, versus 1.6% in patients with high sMAdCAM-1 levels at D0 ($p = 0.01$).

Our study sheds light on the role of sMAdCAM-1 in hematopoietic recovery following allo-HCT through the homing of HSCs to the bone marrow, where they can differentiate and repopulate the blood cell lineages. Importantly, the interaction between MAdCAM-1 and its receptor on HSCs may facilitate the migration of these cells to the bone marrow niche, which is essential for hematopoietic recovery after treatment such as bone marrow transplantation or chemotherapy.[13] Furthermore, some studies have shown that MAdCAM-1 expression was upregulated on bone marrow endothelial cells (ECs) within 24 h post-lethal irradiation,[14,15] suggesting that the conditioning regimen before allo-HCT contributes to HSC engraftment through MAdCAM-1 upregulation on ECs. Interestingly, in phase 3 randomized study evaluating vedolizumab for GvHD prophylaxis after allo-HCT,[9] the median day of neutrophil recovery was delayed in patients that received vedolizumab, being 16.0 (range, 8–35) days in the experimental group versus 15.0 (range, 8–31) days in the placebo group, suggesting that blockade of the MAdCAM-1/α4β7 axis after allo-HCT delayed engraftment.

Furthermore, in the setting of allo-HCT, an association between gut microbial taxa and daily changes in white blood count was reported, further supporting the idea that hematopoiesis and mobilization of HSCs respond to the composition of the gut microbiome.[4] Of note, neutrophil, lymphocyte, and monocyte counts were higher in patients who received an autologous fecal microbiota transfer (FMT) in the first 100 days after neutrophil recovery, compared to allo-HCT patients who did not receive this procedure,[4] indicating that gut microbiota modulation using FMT may allow enhanced hematopoiesis recovery after allo-HCT. Nevertheless, although the associations between the microbiota and hematopoiesis are well established, a mechanistic understanding of how the microbiota and bacteria-derived metabolites directly or indirectly impact hematopoiesis is still limited.

Our study lacks an in-depth analysis of gut microbiota composition and the mechanism of downmodulation of sMAdCAM-1 after antibiotic treatment or dysbiosis remains to be determined. Nevertheless, it was previously reported that oral administration of bacteria of the genus *Enterocloster* was sufficient to downregulate MAdCAM-1 expression through its effects on bile acid metabolism,[5] and bile acids were shown to modulate colonic MAdCAM-1 expression colitis.[16] We can therefore hypothesize that bile acid metabolism may also be involved in the regulation of MAdCAM-1 expression in allo-HCT patients.

Collectively, these results suggest that if the concentration of MAdCAM-1 is associated with gut microbiota diversity and is affected by broad anti-anaerobic spectrum antibiotic treatments, this effect mitigated hematopoietic recovery time. These findings suggest a potential link between antibiotic exposure, altered microbiota composition, and hematopoietic recovery in patients undergoing allo-HCT, highlighting the importance of further investigation into microbiome-targeted interventions, such as FMT.[17]

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AUTHOR CONTRIBUTIONS

All authors listed in the manuscript have contributed substantially to this work. Karen Fadel, Mohamad Mohty, Béatrice Gaugler, and Florent Malard designed the study. Karen Fadel, Lama Siblany, Frederic De Vassoigne, and Béatrice Gaugler, performed the experimental analysis. Karen Fadel and Florent Malard performed the statistical analysis. Razan Mohty, Lama Siblany, Nicolas Stocker, and Florent Malard collected biological and clinical data. Eolia Brissot, Anne Banet, Simona Sestili, Rémy Duléry, Zoé Van de Wyngaert, Laure Ricard, Ramdane Belhocine, Agnès Bonnin, Antoine Capes, Tounes Ledraa, Mohamad Mohty, and Florent Malard provided patient samples and collected clinical data. Karen Fadel and Florent Malard prepared the manuscript and figures for publication. All authors reviewed the manuscript.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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