Biochemical and Biophysical Research Communications 460 (2015) 645–650

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Lack of non-hematopoietic SIRPα signaling disturbs the splenic marginal zone architecture resulting in accumulation and displacement of marginal zone B cells

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ARTICLE INFO

Article history:
Received 5 March 2015
Available online 25 March 2015

Keywords:
Spleen
Macrophage
Marginal zone
B cell

ABSTRACT

Signal regulatory protein α (SIRPα) is an immunoglobulin super family protein predominantly expressed by myeloid but not lymphoid cells, and its role in lymphocyte homeostasis and function is still to be revealed. We demonstrate that mice bearing a mutant SIRPα lacking the cytoplasmic signaling domain (SIRPα MT) had an increased amount of splenic marginal zone (MZ) B cells compared to wild-type controls. Immunohistochemical analysis revealed an increased localization of MZB cells into B cell follicular areas of the white pulp in SIRPα MT spleens. However, we found no signs of an increased MZB cell activation level in MT mice. The immune response to T-independent antigens *in vivo* was slightly increased in SIRPα MT mice while sorted MZB from these mice responded normally to LPS *in vitro*. Bone marrow reconstitution experiments demonstrated that the MZB cell phenotype of SIRPα MT mice was due to lack of SIRPα signaling in non-hematopoietic cells. In contrast, MZ retention of MZ macrophages required hematopoietic SIRPα, while normal distribution of metallophilic macrophages required non-hematopoietic SIRPα signaling. In summary, these data identified SIRPα signaling in non-hematopoietic cells to play an important role in regulating the numbers and positioning MZB cell in the spleen.

1. Introduction

The splenic marginal zone (MZ) is a unique microenvironment, positioned between the lymphoid white pulp and the innate scavenging red pulp, where resident immune cells are exposed to high blood flow [1]. The splenic MZ contains MZ B cells, specialized macrophages such as marginal zone macrophages (MZMs) and marginal metallophilic macrophages (MMMs), granulocytes and dendritic cells (DCs), present in a stromal cell network [2,3]. The MZ B cells are non-recirculating cells restricted to the spleen and are considered to be long lived cells that freely shuttles between the MZ and B cell follicles to deliver antigens to follicular dendritic cells (FDCs) in the B cell follicles [4,5]. MZ B cells are specialized in responding to pathogens in the blood and to thymus-independent (T-I) antigens, but can also participate in thymus-dependent (TD) immune responses by presenting antigens to $CD4^+$ T cells [6,7].

Signal regulatory protein α (SIRPα/SHPS-1/BIT/MFR/P84) is a cell surface receptor of the immunoglobulin (Ig) superfamily, which in its cytoplasmic domain has ITIM regions that can mediate binding of the tyrosine phosphatases SHP-1 and/or SHP-2 [8,9]. SIRPα is highly expressed by myeloid cells, such as neutrophils, macrophages and DCs, but also expressed by non-hematopoietic cells such as endothelial cells, neuronal cells and stromal cells [10–14]. In contrast, expression of SIRPα in lymphocytes is barely detectable [14,15]. Tyrosine phosphorylation of SIRPα can be induced by its ligands CD47 and surfactant proteins A- and D, by integrin-mediated adhesion to extracellular matrix proteins, or by various growth factors [10,14,16–20]. Lack of SIRPα signaling, or lack of the ligand CD47, results in a reduced number of $CD11b^+CD4^+$ DCs in the

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http://dx.doi.org/10.1016/j.bbrc.2015.03.084
0006-291X/

splenic MZ, in the small intestinal lamina propria, and in mesenteric lymph nodes [12,21–23]. Although SIRPα is not expressed by T cells, we have found that hematopoietic SIRPα is important for the homeostasis of T cells in the spleen [15].

Despite the finding that SIRPα is important in maintaining normal numbers of MZ DCs, it is unknown if SIRPα signaling has an effect on other leukocytes of the splenic MZ. Therefore, we here investigated MZ B cells and macrophages in SIRPα-mutant mice, in which the extracellular SIRPα-domain is expressed but where most of the cytoplasmic signaling domain is deleted [24].

2. Materials and methods

2.1. Mice

C57BL/6 *SIRPα* mutant (MT) mice, lacking most of the SIRPα cytoplasmic domain have been previously described [24]. C57BL/6 Ly5.1 mice were from Taconic, Italy. All the experiments were performed in compliance with relevant Swedish and institutional laws and guidelines and approved by the Umeå research animal ethic committee (A14-12).

2.2. Flow cytometry

Splenocytes were prepared by mechanical disruption and incubated with unlabeled anti-CD16/CD32 (2.4G2) for 15 min to block Fcγ receptors, followed by anti-mouse CD23PE (BD biosciences-B3B4), CD21FITC (eBioscience-8D9), B220- biotin (Biolegend-RA3-6B2), CD19APC (BD biosciences-1D3), CD1d-biotin (Biolegend-1B1), CD80-Biotin (Biolegend-16-10A1), CD86-biotin (Biolegend- GL-1), CD40-biotin (Biolegend- 3/23), or MHC-class II (Biolegend- M5/114.15.2), as indicated in the figures. Biotin-conjugated mAbs were detected with streptavidin-APC (Immunotools) before analysis using FACS Calibur or LSR II (BD biosciences) and Cell Quest or FACSDiva software (BD biosciences).

2.3. Immunohistochemistry

Cryosections (8 μm) from spleens frozen in Tissue Tek (Sakura) were air-dried, rehydrated in PBS, fixed in 2% paraformaldehyde and blocked with 10% goat serum. Sections were incubated with antibodies against MOMA-1 (a generous gift from Dr. Pieter Leenen, Erasmus University, Rotterdam, Netherland) or MARCO (AbD Serotec), followed by Alexa 594 anti-rat IgG (BD biosciences). Further sections were incubated with biotin-conjugated anti-CD1d (Biolegend) followed by fluorophore tyramide (PerkinElmer) and analyzed by laser scanning confocal microscopy (Leica TSP-2, Heidelberg, Germany), Leica-LCS software (Leica, Heidelberg, Germany) and Adobe Photoshop CS4.

2.4. Immunizations and antigen-specific ELISA

Pre-immune serum was collected on the day before i.v. immunization with 10 μg TNP-ficoll or TNP- LPS (Biosearch Technologies). Seven or eight days later, serial dilutions of sera were analyzed for TNP specific IgM or IgG_3 antibodies by ELISA. The plates were

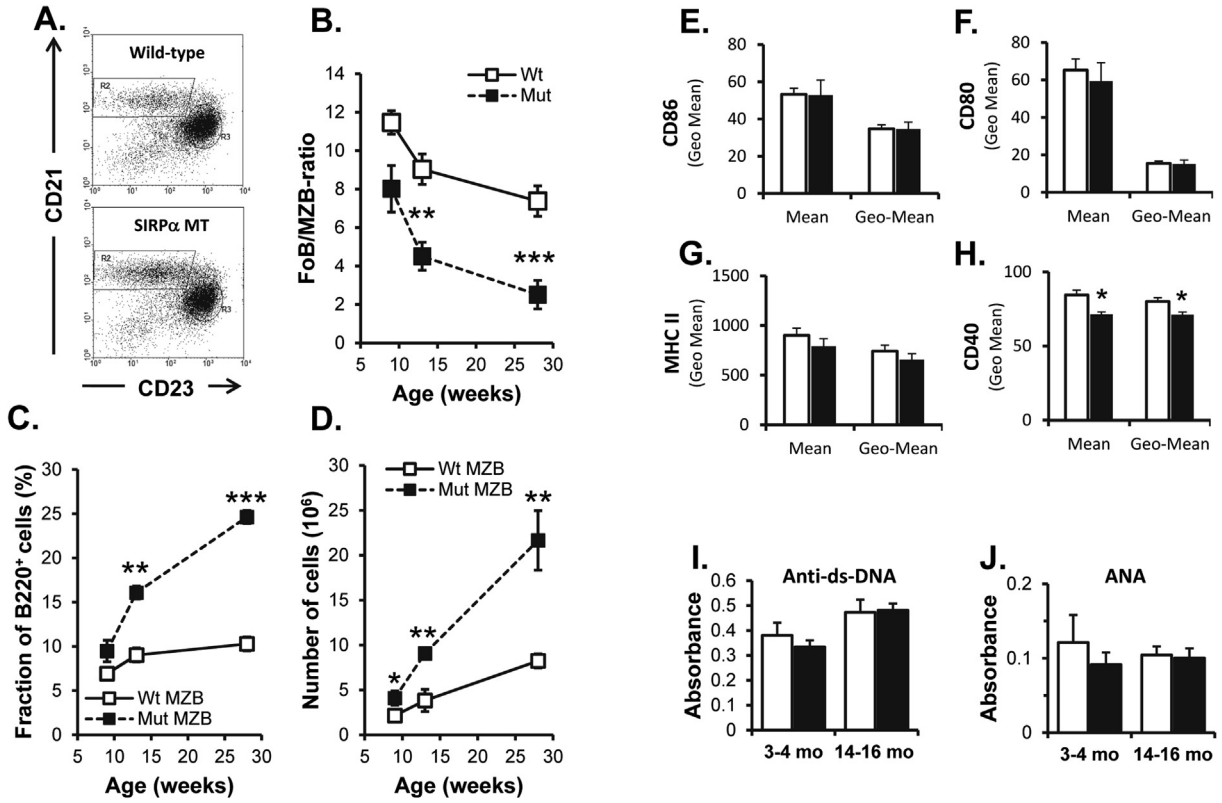

Fig. 1. Accumulation of non-activated MZB cells and lack of autoantibodies in SIRPα MT mice (A) Splenic $B220^{+}CD21^{int}CD23^{hi}$ FoB cells and $B220^{+}CD21^{hi}CD23^{lo}$ MZB cells were separated using flow cytometry. (B) The FoB/MZB-ratio was reduced with increasing age in SIRPα MT mice (Mut-filled symbols), as compared with that in Wt mice (Wt-open symbols). (C) Fraction of MZB cells out of total $B220^{+}$ cells, and (D) absolute numbers of MZB cells, in Wt (Wt-open symbols) and SIRPα MT mice (Mut-filled symbols) at increasing age. Data are means ± SD for 3-5 mice/group. Expression of (E) CD86, (F) CD80, (G) MHC II and (H) CD40 in MZB cells of 13 weeks old Wt (Wt-open bars) and SIRPα MT mice (Mut-filled bars) quantified using flow cytometry. Shown are the mean and geometric mean fluorescent intensities for each marker. Data are means ± SD for 3 mice/group. Sera from 3 to 4 or 14–16 months old Wt (open bars) or SIRPα MT mice (black bars) were collected and assayed for (I) anti-ds-DNA or (J) anti-nuclear antigens (ANA), using ELISA. Data are means ± SEM for 5-6 mice/group. *P < 0.05, **P < 0.01 and ***P < 0.001, as compared with that in Wt mice, using Student's t-test for unpaired analyses.

developed using pNPP-substrate (Sigma) and absorbance at 405 nm was analyzed, using an ELISA-plate reader (Molecular Device) and SoftMax pro software (Molecular Device).

2.5. In vitro B-cell stimulation assays

Erythrocyte-free spleen cell suspensions were incubated with unlabeled anti-CD16/CD32 for 15 min. After labeling with antibodies against CD23, CD21 and CD19, MZB cells were sorted to more than 95% purity on a FACS ARIA-III cell sorter (BD Bioscience) and incubated for 3 days at 1×10^5 cells/well into 24-well flat-bottom plates with 1 or 10 μg LPS/ml (Sigma). Supernatants were then collected and assayed for IgM by ELISA.

2.6. Bone marrow reconstitution

Ly5.1 recipient mice were lethally irradiated by exposure to 5 Gy at two occasions separated by 3 h, followed by intravenous injection of 5×10^6 Ly5.2 wild-type (Wt) or SIRPα MT bone marrow cells 3 h later. Similarly, lethally irradiated Ly5.2 Wt or SIRPα MT mice were reconstituted with 5×10^6 Ly5.1 Wt bone marrow cells. At the time of analysis, more than 97% of all splenic leukocytes were of donor origin (data not shown).

2.7. In vitro chemotaxis assay

For analysis of *in vitro* chemotaxis, 5×10^5 splenocytes in RPMI 1640 + 5% FCS were seeded in the upper chamber of 3 μm transwell inserts (Corning Costar) placed in wells containing medium alone, 100 nM S1P (Sigma Aldrich) or 1 μg/ml CXCL13 (PeProTech) for 2 h at 37 °C and 5% CO_2. Transmigrated cells were stained with antibodies against B220, CD21 and CD23, and quantified using flow cytometry (FACSCalibur).

2.8. Autoantibody assay

Serum levels of anti-nuclear antigens (ANA) were quantified using ELISA (Alpha Diagnostics International), following the manufacturer's instructions. For detection of anti-ds-DNA antibodies, ELISA plates (Nunc MaxiSorp) were coated with methylated BSA in PBS at 4 °C overnight, washed with ELISA wash [NaCl (0.15 M), Tween 20 (0.05%), dH_2O] and coated with calf thymus DNA in PBS overnight at 4 °C. Coated plates were washed and blocked with PBS/1% BSA for 2 h before adding diluted sera (1:100) for 2 h at room temperature. Bound antibodies were detected with AP-conjugated secondary antibodies (Southern Biotech), developed using pNPP-substrate (Sigma), and absorbance at 405 nm was analyzed using an ELISA-plate reader (Molecular Device) and Softmax Pro software (Molecular Device).

2.9. Statistics

Two-tailed Student's *t*-test for unpaired analysis was used as described in the figure legends.

3. Results

3.1. SIRPα signaling-deficient mice have an expanding population of non-activated MZB cells

When analyzing $B220^+CD23^{hi}CD21^{int}$ FoB cells and $B220^+CD23^{lo}CD21^{hi}$ MZB cells (Fig. 1A), we found a decreased FoB/

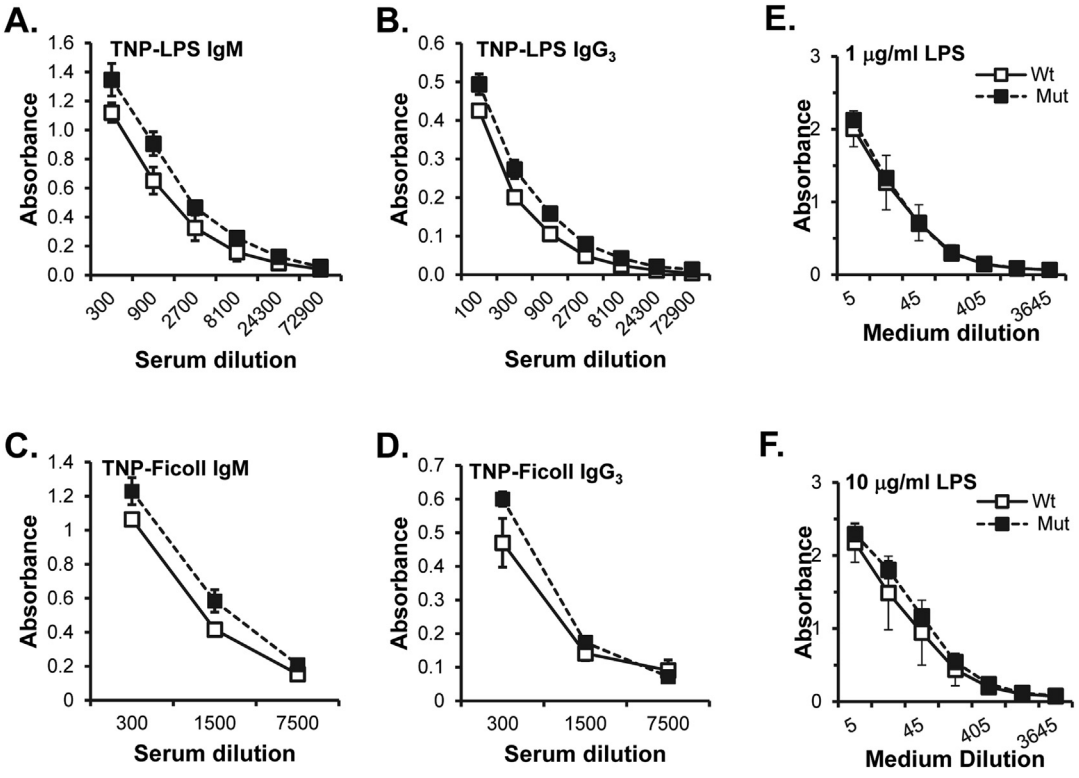

Fig. 2. Immune responses to T-independent antigens in SIRPα MT mice Wt (open symbols) or SIRPα mutant mice (black symbols) were challenged with 10 μg of TNP-LPS (A, B) or TNP-Ficoll (C, D) and the levels of TNP-specific IgM (A, C) or IgG_3 (B, D) antibodies were determined by ELISA at 7 or 8 days after immunization. Data are means ± SEM for 4-6 mice of each genotype. (E, F) FACS-sorted MZB cells from Wt (open symbols) or SIRPα MT mice (black symbols) were stimulated with LPS at (E) 1 or (F) 10 μg/ml for 3 days before culture supernatants were collected and assayed for IgM by ELISA. Data are means ± SD for 3 experiments/group.

MZB cell-ratio in spleens of SIRPα MT mice, as compared with that in Wt spleens (Fig. 1B). The fraction (Fig. 1C) as well as the absolute number of MZB cells per spleen (Fig. 1D) was significantly increased in spleens of SIRPα MT mice at 13 or 28 weeks of age, as compared with that in age-matched Wt controls. An increased MZB cell population in SIRPα MT mice was further confirmed by quantification of $CD19^{+}CD1d^{hi}$ MZB cells (data not shown). Activation of MZB cells is associated with an increased expression levels of CD80, CD86, MHC class II and CD40 [5]. However, Wt and SIRPα MT MZB cells expressed similar levels of CD86, CD80 or MHC class II (Fig. 1E–G) while the expression of CD40 was slightly reduced in SIRPα MT MZB cells (Fig. 1H). Since an expanded MZB cell population has been linked to the pathogenesis of autoimmune disease in some murine models [25,26], we analyzed sera of Wt and SIRPα MT mice for anti-ds-DNA or ANA. This analysis revealed no signs of an increased autoantibody or ANA level in SIRPα MT mice up to 16 months of age (Fig. 1I and J).

3.2. Immune responses to T-independent antigens in SIRPα MT mice in vivo or in isolated MZB cells in vitro

Since MZB cells primarily respond to thymus-independent (T-I) antigens, we investigated the response to TNP-LPS or TNP-Ficoll in Wt or SIRPα MT mice. MT mice responded with slightly higher levels of IgM and IgG_3 antibodies to both these antigens, as compared with that in Wt mice (Fig. 2A–D). To investigate if this slightly increased response to T-I antigens in SIRPα MT mice was intrinsic to the MZB cells, we stimulated equal numbers of FACS-sorted Wt or SIRPα MT MZB cells with LPS (1 or 10 μg/ml) for 3 days *in vitro*, but observed equal IgM production by both Wt and MT MZB cells in response to either dose of LPS (Fig. 2E and F).

3.3. MZB cells are displaced from the MZ in SIRPα MT mice

In Wt spleens, $CD1d^{hi}$ MZB cells were preferentially present in the MZ co-localizing with $MARCO^{+}$ MZMs (Fig. 3A). However, in SIRPα MT spleens, a large amount of the MZB cells were localized in the B cell follicles and MZMs were not strictly organized within the MZ but appeared to be redistributed into the red pulp areas (Fig. 3A). Similarly, MOMA-1^{+} MMMs were not contained in their normal location on the white pulp side of the marginal sinus in SIRPα MT spleens, but were found to extend into the MZ (Fig. 3B). MZB cells are attracted to the MZ by their chemotactic response to sphingosine 1-phosphate (S1P), which can overcome CXCL13-stimulated recruitment of MZB cells into the B cell follicle [4,27]. To test if the increased follicular localization of MT MZB cells was due to a defect in the chemotactic responses to S1P or CXCL13, we next analyzed the migration of MZB cells towards these two factors *in vitro*. These experiments showed that the migration of Wt and MT MZB cells was equal in response to either S1P or CXCL13 (Fig. 3C).

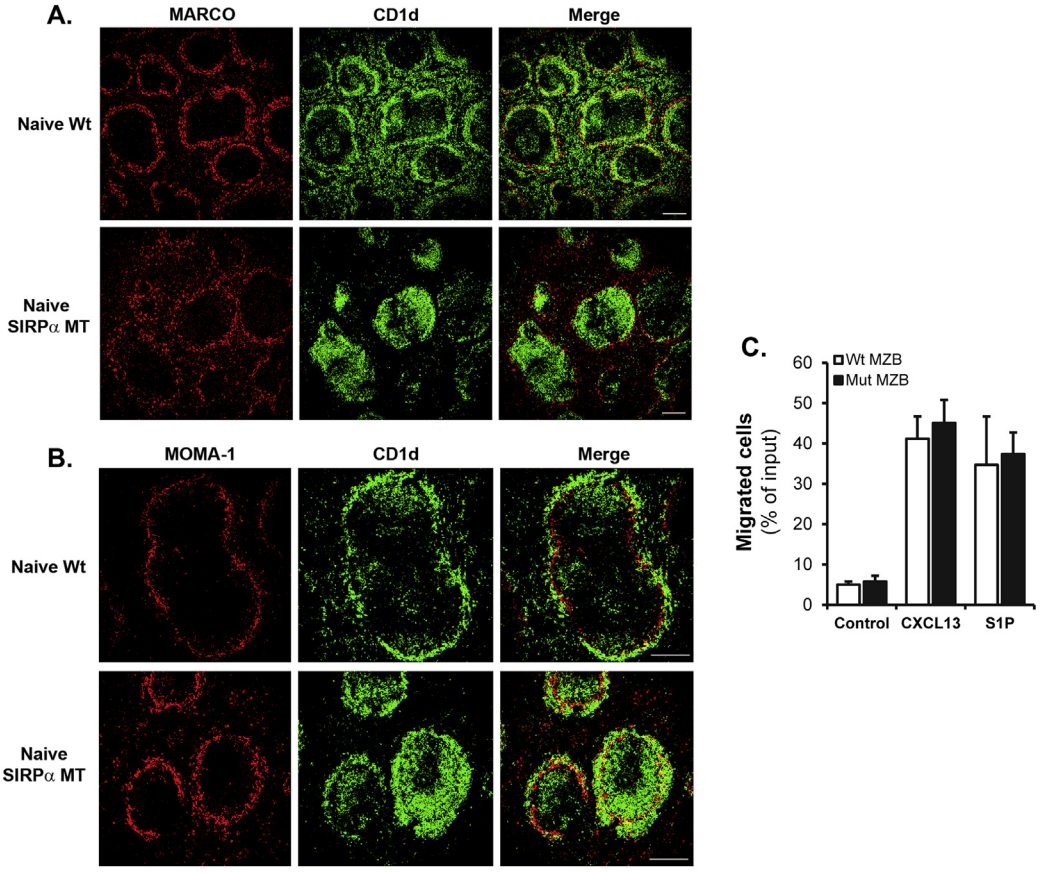

Fig. 3. Increased follicular localization of MZB cells in SIRPα MT mice (A) Spleens of Wt or SIRPα MT mice were stained for MARCO (red) to detect MZM and CD1d (green) to detect $CD1d^{hi}$ MZB cells. Scale bar represents 200 μm. (B) Spleens of Wt or SIRPα MT mice were stained for MOMA-1 (red) to detect MMM and CD1d (green) to detect $CD1d^{hi}$ MZB cells. Scale bar represents 50 μm. (C) Chemotaxis of MZB cells from Wt (open bars) or SIRPα MT mice (black bars) towards S1P (100 nM) or CXCL13 (1 μg/ml) *in vitro*. Data are means ± SD from two separate experiments with duplicate samples for each genotype in each experiment.

3.4. Non-hematopoietic SIRPα signaling is required to maintain normal numbers and normal localization of MZ B cells

To investigate if the MZB cell phenotype of SIRPα MT mice was due to the lack of SIRPα signaling in the hematopoietic or non-hematopoietic compartment, we analyzed Wt → Wt, SIRPα MT → Wt or Wt → SIRPα MT bone marrow-chimeric mice. While the number of MZB cells per spleen was similar in Wt → Wt and SIRPα MT → Wt chimeras (Fig. 4A), MZB cells were increased by 60% in Wt → SIRPα MT chimeras, as compared with that in Wt → Wt chimeras (Fig. 4B). MZB cells were normally positioned in the MZ in spleens of both Wt → Wt and SIRPα MT → Wt chimeras (Fig. 4C and D). However, in Wt → SIRPα MT chimeras MZB cells were normally present in the MZ but also localized into the B cells follicles to a larger extent (Fig. 4C and D). Since lack of non-hematopoietic SIRPα signaling *per se* resulted in a MZB cell phenotype resembling that of naïve SIRPα MT mice, we next evaluated the distribution of MARCO$^+$ MZMs and MOMA-1$^+$ MMMs in these mice to understand if that also mimicked that observed in spleens of naïve SIRPα MT mice. In contrast to that in naïve MT mice (Fig. 3A), MARCO$^+$ MZMs were normally localized to the MZ in spleens of Wt → SIRPα MT chimeras (Fig. 4C), while MOMA-1$^+$ MMMs showed a broader distribution in the MZ of Wt → SIRPα MT spleens, similar to that in naïve SIRPα MT mice (Fig. 4D). However, in SIRPα MT → Wt chimeras, MZMs showed the same disorganized distribution as seen in naïve MT mice (Fig. 4C).

4. Discussion

We here found that lack of SIRPα signaling in mice results in an expanded MZB cell population. However, several findings indicated that the expanded MZB cell population in SIRPα MT mice was not associated with an increased activation level. First, the expression levels of CD80, CD86, MHC class II or CD40 were not increased. Second, we found no increased levels of autoantibodies in MT mice up to 16 months of age. Third, purified MT MZB cells did not show an increased response to LPS *in vitro*. MZB cells respond rapidly to TI antigens and we hypothesized that such responses would be increased in the MT mice. Surprisingly, the immune response to TNP-LPS or TNP-Ficoll was not much enhanced in SIRPα MT mice. This could likely be explained by the finding that a substantial amount of the MZB cells showed an increased localization to the B cell follicles of MT spleens, which would reduce their exposure to blood antigens.

Since SIRPα is expressed by both myeloid cells and non-hematopoietic mesenchymal cells [9,11], we used bone marrow chimeras to investigate if lack of SIRPα signaling in any of these compartments could explain the MZB cell phenotype of MT mice. Lack of SIRPα signaling in the hematopoietic compartment only resulted in normal MZB cell numbers and normal localization to the MZ. However, lack of SIRPα signaling in radiation-resistant non-hematopoietic cells resulted in an increased number of MZB cells and increased follicular localization of these cells. Thus, although the exact mechanisms are unclear, SIRPα signaling in non-hematopoietic cells appears to be required to prevent expansion of MZB cells.

The localization of MZB cells into the MZ has been suggested to be regulated by several mechanisms. This B cell subset express S1P-receptors which mediates the migration of MZB cells towards the high concentration of the lysophospholipid S1P present in blood [27]. In contrast, activated MZB cells down-regulate S1P receptors and instead migrate into the B cell follicles in response to CXCL13

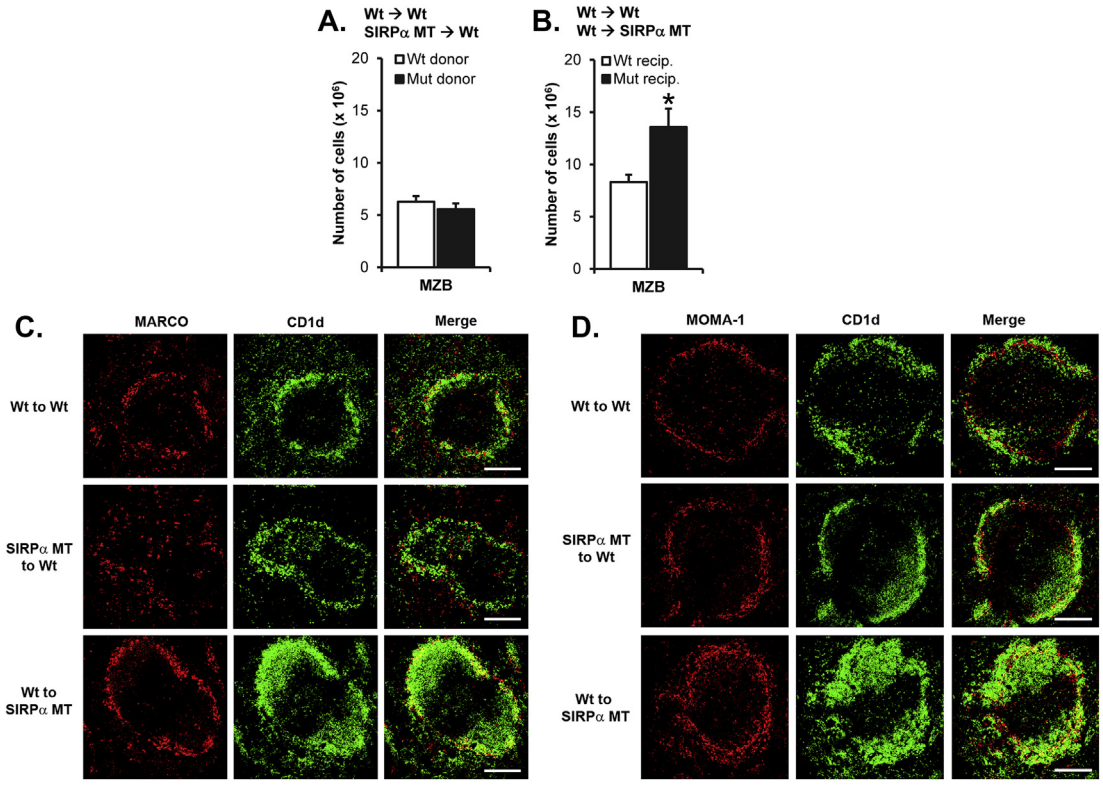

Fig. 4. Non-hematopoietic SIRPα is required to maintain normal numbers and normal localization of MZ B cells Absolute numbers of CD19$^+$CD21^{high}CD23^{low} MZB cells in the spleens of (A) Wt→Wt and SIRPα MT→Wt chimeras (6 mice/group), or (B) Wt→Wt and Wt→SIRPα MT chimeras (5 mice/group) at 20 weeks after bone marrow reconstitution. *P < 0.05, using Student's t-test for unpaired analyses. (C, D) Spleen sections of chimeric mice were stained for MARCO (red, C) to detect MZMs, MOMA-1 (red, D) to detect MMMs and CD1d (green) to detect CD1d^{hi} MZB cells. Scale bar represents 50 μm.

[27]. However, the increased white pulp localization of SIRPα MT MZB cells was not due to a defect in the migration to either S1P or CXCL13. It has also been suggested that MZMs can function to retain MZB cells in the MZ, since antibodies blocking the MZM receptor MARCO, or uptake of *Staphylococcus aureus* by MZMs, results in re-localization of this macrophage subset into the splenic red pulp while MZB cells are migrating into the B cell follicle [28]. Thus, an increased localization of MT MZB cells into the B cell follicles could be due to the fact that MZMs were present to a lesser extent in the MZ and were more localized in the red pulp area of naïve SIRPα MT spleens. However, although MZB cells showed an increased follicular localization in Wt → SIRPα MT chimeras, MZMs localized normally to the MZ, suggesting that the follicular MZB cell localization in naïve MT mice was unlikely mediated by lack of MZMs in the MZ. Unexpectedly, we found that the reorganized distribution of MZMs seen in naïve MT mice was also present in SIRPα MT→Wt chimeras, suggesting that lack of SIRPα signaling in this macrophage subset is required for their MZ localization. The normal MZ localization of MZB cells in MT→Wt chimeras obviously contradicts the assumption that MZMs are necessary to retain MZB cells in the MZ. However, CCL-19/CCL-21-deficient *plt/plt*-mice show a strong reduction of MZM but maintained localization of MZB cells in the MZ [29], suggesting that lack of MZM may not always result in displacement of MZB cells.

MOMA-1^+ MMMs, normally located between the MZ and the B cell follicle, were present in the whole MZ of naïve SIRPα MT spleens. This widened distribution of MMMs was also maintained in Wt → SIRPα MT chimeras. Interestingly, mice deficient in one of the receptors for S1P, $S1P_3$, also show a widened distribution of MMMs and an increased follicular localization of MZB cells [30]. Thus, a similar distribution of MMMs in SIRPα MT spleens could possibly explain the increased amount of MZB cells in B cell follicles of these mice.

Further studies are required to understand the details of the non-hematopoietic cell type(s) that require SIRPα signaling to regulate the number and positioning of MZB cells and a normal positioning of MMMs.

Author disclosure

The authors declare no competing financial interests.

Conflict of interest

None.

Acknowledgments

We thank Ms Barbro Borgström, Dr. Jannek Hauser, Ms Radha Thyagrajan for excellent technical assistance.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.bbrc.2015.03.084.

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