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# Defining the role of CD47 and SIRPα in murine B cell homeostasis

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**Abstract**

B cell development is a highly organized process, which commences in the fetal liver during embryogenesis and in the bone marrow (BM) after birth. Surface $IgM^+$ immature B cells emigrate from the BM via the blood stream to the spleen and finally differentiate into conventional mature follicular B (FoB) cells and marginal zone (MZ) B cells. Conversely, some $sIgM^+$ immature B cells can also mature into $IgD^+$ FoB cells in the BM. The ubiquitously expressed cell surface glycoprotein CD47 and its receptor signal regulatory protein α (SIRPα) are members of the immunoglobulin superfamily. Both individually and upon their interaction, CD47 and SIRPα have been found to play important role in the homeostasis of T lymphocytes or $CD8^-$ conventional dendritic cells (cDCs) in secondary lymphoid organs. However, their role in regulating B cell homeostasis has remained unknown. The present study describes important roles of CD47 and SIRPα in B cell homeostasis. Lack of SIRPα signaling in adult SIRPα mutant (MT - cytoplasmic domain deletion) mice resulted in an impaired B cell maturation in the BM and spleen, which was also reflected in the blood. In the BM and spleen of SIRPα MT mice, reduced numbers of semi-mature $IgD^+IgM^{hi}$ follicular type-II (F-II) and mature $IgD^+IgM^{lo}$ follicular type-I (F-I) B cells were observed, while earlier BM B cell progenitors or splenic transitional B cells remained unaltered. In SIRPα MT mice, maturing B cells in BM and spleen were found to express higher levels of the pro-apoptotic protein BIM and contained an increased level of apoptotic cells. In contrast to that for FoB cells, the splenic MZ B cell population was increased with age in SIRPα MT mice without showing an increased level of activation markers. Immunohistochemical analysis revealed an increased follicular localization of MZ B cells in the spleens of SIRPα MT mice. In addition, MZ macrophages and marginal metallophilic macrophages were not restricted to their normal position in SIRPα MT spleens. Interestingly, CD47-deficient (*CD47*$^{-/-}$) mice mimicked the FoB cell phenotype observed in SIRPα MT mice and had a reduced number of FoB cells in the BM, blood and the spleen at 5-6 months of age, but not in younger mice. Similar to SIRPα MT mice, *CD47*$^{-/-}$ mice also displayed an increased number of splenic MZ B cells. Sera form both mouse strains did not show any signs of an increased production of autoantibodies or antinuclear antigens. BM reconstitution experiments identified a requirement for non-hematopoietic SIRPα signaling for normal B cell maturation in the BM and to maintain normal numbers and retention of MZ B cells in the splenic MZ. On the contrary, hematopoietic SIRPα signaling appeared to be important for FoB cell maturation in the spleen. Interestingly, hematopoietic SIRPα was required for normal MZ retention of MZ macrophages while normal distribution of metallophilic macrophages required non-hematopoietic SIRPα signaling. Collectively, these findings revealed an important role of CD47 and of SIRPα signaling in B cell homeostasis in different lymphoid organs.

**Keywords:** B cells, CD47, Signal regulatory protein α, Follicular B cells, Marginal zone B cells

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