Regulation of human dendritic cells by B cells depends on the signals they receive

B cells are classically known for producing antibodies. However, several reports also indicate that B cells are potent regulators of immune responses including those mediated by dendritic cells (DCs), although direct effect of B cells on DC was relatively unexplored.1-4 Recently, Morva et al demonstrated that CD40 + TLR9 (CpG)–stimulated human B cells restrain the differentiation of monocyte-derived DCs and their maturation.5 They further found that stimulation of B cells is necessary to trigger potent regulatory activities on DCs.

Under physiological conditions, there is a constant cross-talk between DCs and B cells. Although suppression of DCs may play a role in preventing the autoimmunity, normal functioning of DCs without suppression is also critical for immune homeostasis and immune response to tumor cells and foreign antigens. These views indicate that B cells are not continually inhibitory on DCs. As B cells can receive activation signals via diverse receptors including B-cell receptor (BCR), CD40 and TLR, we surmised that the effect of stimulated B cells on DCs depends on the type of signals they receive. In view of the importance of BCR signaling in B-cell activation and in generation of regulatory B cells,1,2 we explored the role of BCR-stimulated B cells either alone or in combination with TLR9 stimulation on the differentiation and maturation of DC.

We found that when monocytes were differentiated into DCs in the presence of cytokines GM-CSF and IL–4 and B cells that were activated by combination of BCR + TLR9 (CpG) stimuli, there was a significant reduction in the expression of DC markers such as DC-SIGN, CD83, HLA-DR, CD40, CD80, CD86, and CD58 (Figure 1A). Thus, in accordance with Morva et al.,3 our results revealed a regulatory role of BCR + CpG-stimulated B cells on differentiation of DCs. However, B cells that received signals only via BCR were not inhibitory (Figure 1A), indicating that in the absence of TLR stimuli, activated B cells do not block differentiation of DCs. In addition, we report a novel mechanism of modulation of DCs by regulatory B cells. We found that BCR + CpG-stimulated B cells induce a high percentage of apoptosis in differentiating DCs (Figure 1B). Thus, regulatory B cells can modulate DC-mediated immune responses by controlling the number of DCs. Of note, Fas-FasL–mediated apoptosis of target cells is proposed to be one of the mechanisms of immune regulation by regulatory B cells.1

Furthermore, with profound inhibition of LPS-mediated maturation of DCs by CD40 + CpG-activated B cells,5 we found that B cells that received BCR signaling alone were only partially inhibitory on DCs (Figure 1C). Together, our results indicate that regulation of DC differentiation and maturation by B cells depends on the type of stimuli they receive. B cells receiving BCR stimulation alone are not inhibitory on DCs while under inflammatory conditions as in TLR9 stimulation; these TLR-9–stimulated B cells can act as inflammation-limiting factors in part via inhibition of DC activation. These functional differences of B-cell stimuli were also reflected in their ability to induce the expression of key molecules CD62L and CD80/CD86 on B cells (Figure 1D) that are proposed to be important in the regulation of DC and T-cell functions, respectively, by regulatory B cells.5,6

Mohan S. Maddur
Inserm Unité 872,
Centre de Recherche des Cordeliers,
Equipe 16–Immunopathology and therapeutic immunointervention,
Université Pierre et Marie Curie,
Université Paris Descartes, Unité Mixte de Recherche 872, Inserm,
Paris, France

Sriini V. Kaveri
Inserm Unité 872,
Centre de Recherche des Cordeliers,
Equipe 16–Immunopathology and therapeutic immunointervention,
Université Pierre et Marie Curie,
Université Paris Descartes, Unité Mixte de Recherche 872, Inserm,
Paris, France;
International Associated Laboratory IMPACT
(Inserm France–Indian Council of Medical Research, India),
National Institute of Immunohaemotology,
Mumbai, India

Jagadeesh Bayry
Inserm Unité 872,
Centre de Recherche des Cordeliers,
Equipe 16–Immunopathology and therapeutic immunointervention,
Université Pierre et Marie Curie,
Université Paris Descartes, Unité Mixte de Recherche 872, Inserm,
Paris, France;
International Associated Laboratory IMPACT
(Inserm France–Indian Council of Medical Research, India),
National Institute of Immunohaemotology,
Mumbai, India

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Correspondence: Jagadeesh Bayry, Inserm Unité 872, Equipe 16–Centre de Recherche des Cordeliers, 15 rue de l’Ecole de Médecine, Paris, F-75006, France; e-mail: jagadeesh.bayry@crc.jussieu.fr.
Recent data indicate that NOTCH1 mutations significantly increase the risk of CLL progression toward Richter syndrome (RS) and chemoresistance,1,2 and that activation of NOTCH1 at time of CLL diagnosis is an independent prognostic factor of poor survival.1,3 We report here a case of CLL with a novel rearrangement of NOTCH1 identified at the time of RS. The patient, a 58-year-old male, was diagnosed with CLL (unmutated VH) in RS in June 2003. Cytogenetic analysis and FISH on peripheral blood (PBL), bone marrow (BM), and lymph node (LN) cells showed 2 related clones: one with an isolated t(14;12) and a second with new additional karyotypic changes, were seen in the analyzed BM (06/2011) and BM revealed an evolved clone with complex aberrations including t(14;19)(q32;q13)/IGH-BCL3 and t(12;19)negative BCL3. The patient was treated and achieved complete remission and was treated with rituximab, fludarabine, and cyclophosphamide followed by a 6-month maintenance protocol with rituximab. The patient had a 2-year progression-free survival.

To the editor:

Rearrangement of NOTCH1 or BCL3 can independently trigger progression of CLL

Recent data indicate that NOTCH1 mutations significantly increase the risk of CLL progression toward Richter syndrome (RS) and chemoresistance, and that activation of NOTCH1 at time of CLL diagnosis is an independent prognostic factor of poor survival. We report here a case of CLL with a novel rearrangement of NOTCH1 identified at the time of RS. The patient, a 58-year-old male, was diagnosed with CLL (unmutated VH) in RS in June 2003.

Cytogenetic analysis and FISH on peripheral blood (PBL), bone marrow (BM), and lymph node (LN) cells showed 2 related clones: one with an isolated t(14;12) and a second with new additional karyotypic changes, including t(14;19)(q32;q13)/IGH-BCL3 and t(12;19)negative BCL3. The patient was treated and achieved complete remission and was treated with rituximab, fludarabine, and cyclophosphamide followed by a 6-month maintenance protocol with rituximab. The patient had a 2-year progression-free survival.

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