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Peripheral expression of RAG in human B lymphocytes in normal and pathological conditions is dependent on interleukin-6☆

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Abstract

Establishment of the B cell repertoire is regulated by recombination activating genes RAG1 and RAG2 proteins in the bone marrow. Tolerance of autoreactivity is mainly prevented by receptor editing, i.e. synthesis of a new B cell receptor following re-expression of RAG1 and RAG2. Numerous signals can lead to RAG up-regulation, all in association with soluble cytokines. In the periphery, autoreactive B cells or low-affinity B cell receptor synthesis may appear following antigenic immune response. Receptor revision, i.e. new immunoglobulin gene rearrangement can participate to the control of these lymphocytes following new RAG1 and RAG2 re-induction. Though signals leading to this peripheral RAG up-regulation are poorly described, IL-6 seems to have a preponderant role. Therefore, the elevated levels of IL-6 secreted by activated B cells in systemic lupus erythematosus might contribute to the maintenance of abnormal RAG expression, and in turn may participate to the emergence of autoreactive B cells in the periphery.

Keywords: B lymphocytes; Recombination activating gene; IL-6; Autoreactivity

Contents

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1. RAG is not dispensable for B cell maturation

1.1. Numerous signals are involved

The B cell repertoire is shaped in the bone marrow during early ontogenesis. It is progressively constituted through the rearrangements of randomly selected immunoglobulin (Ig) variable genes. These recombination process are regulated by the recombination activating gene (RAG) 1 and RAG2 products [1] of which their absence impede the maturation of the B cell lymphopoiesis [2]. Interestingly, expression of these enzymes is modulated by environmental factors, so that they are not constitutively expressed but instead up-regulated according to the maturation status of the B cells. Thus, the early stages of B cell differentiation require IL-7 which influences Ig gene rearrangements [3] and regulates RAG expression in association with CD19 [4]. Two signals are required for the RAG gene up-regulation, one mediated by direct cell contact with stromal cells and one due to soluble cytokines [5].

Later in the periphery, RAG-positive B cells can be detected in germinal centers of secondary lymphoid organs in mice as well as in humans [6–8]. Again, at least two signals are necessary including either CD40L [9], LPS [6], or SAC I [10] and cytokines.

1.2. Cytokines are consistently required

It is interesting to note that in all models, cytokines seem absolutely necessary, though they may vary from one model to another depending on the first signal. While IL-7 is indispensable for the early stage of B cell development [4], IL-3 and IL-6 can activate RAG gene transcription in lymphoid progenitor cells following interactions with bone marrow stromal cells [5]. Similarly, IL-7 is required in association with CD40L for RAG up-regulation in mature splenic mice B cells [9], whilst IL-4 triggers their expression when such cells are stimulated with LPS [6]. IL-2 can also provide the soluble signal when human blood B cells are activated by SAC I [10].

1.3. The specificity of IL-6

As mentioned above, IL-6 influences RAG expression in the early stage of B cell differentiation. However, no data are available to date concerning the involvement of IL-6 in the control of RAG up-regulation in mature B cells. We previously reported that mature human B cells outside germinal centers may express RAG1 and RAG2

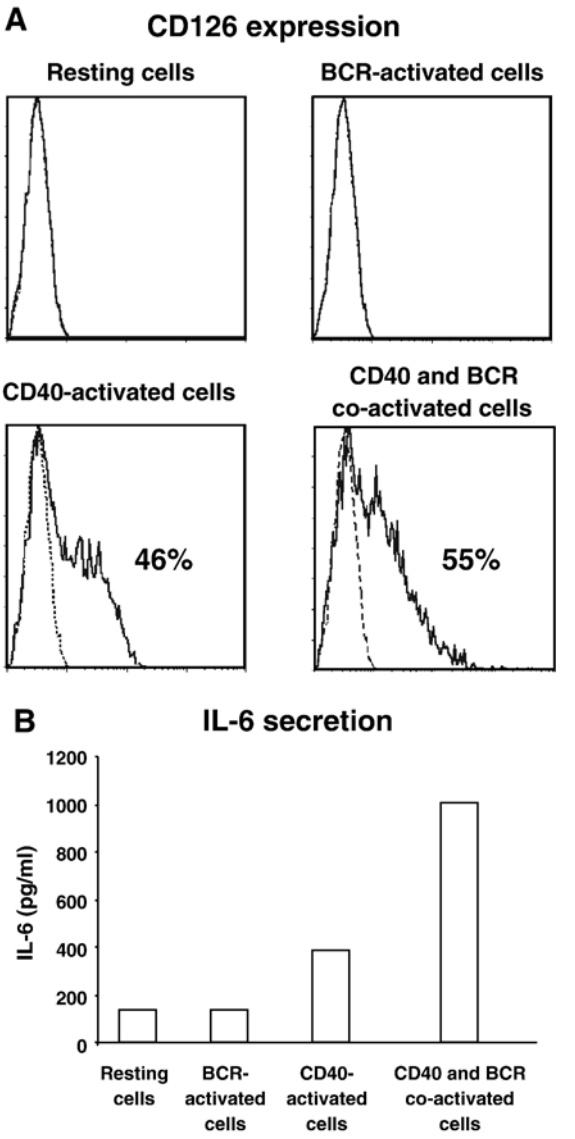

Fig. 1. CD126 and IL-6 induction on human activated B cells. Tonsillar B cells were stimulated for 24 h with 10 μg/ml anti-IgM or for 5 days on CD40L-transfected fibroblasts with or without 1 μg/ml anti-IgM. Expression of CD126, the alpha-chain of IL-6 receptor was analyzed by flow cytometry (A), and the concentration of IL-6 in supernatants determined by ELISA (B).