Retinoic-Acid-Induced Enhancing Effects of Immunoglobulin Synthesis by Human B Cells

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Key Words

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Retinoic acid (RA) has attracted considerable attention as an agent with a broad range of physiologic and metabolic effects [1]. RA and its parent compound, retinol (ROH, vitamin A) have been recognized as immunopotentiating agents since the early 1900s; their importance in the susceptibility of vitamin-A-deficient animals and humans to infection is well known. A number of studies have focused on the immunomodulating effects of vitamin A [2, 3]. Over the past several years, our laboratory has studied the effects of RA on immunoglobulin (Ig) synthesis by cord blood mononuclear cells (CBMCs) [4-6]. We have shown that the stimulation of CBMCs with formalinized Cowan I strain *Staphylococcus aureus* (SAC), which is dependent on T cells or soluble T cell factors for inducing the differentiation of B cells into Ig-secreting cells, produced a 2- to 47-fold augmentation in IgM synthesis. Using an ELISA spot assay, we could show that this RA-induced enhancement in Ig synthesis was due to the 'recruitment' of more B cells to differentiate into Ig-secreting cells, and not to increased Ig synthesis by a single B cell. Preincubation of highly purified T cells from CBMCs for 36 h with RA augmented the IgM synthesis of an enriched B cell fraction. Incubation of enriched B cells (containing B cells and monocytes, and less than 0.5% T cells) with SAC produced a 4- to 5-fold augmentation in IgM synthesis compared to supernatants obtained from wells without SAC, which suggested that RA had a direct effect on B cells (and/or monocytes). To determine whether RA can act directly on B cells to induce augmentation in Ig synthesis, the effects of RA on Epstein-Barr virus (EBV)-transformed B cell lines was examined. The addition of RA to established EBV-transformed adult human B cell lines produced an increase in IgM synthesis (mean fold increase: 5.3 ± 2.1 , range 3.8-7.7; $p < 0.05$). These data suggest that RA can have a direct effect on B cells. The increased Ig secretion by the EBV cell lines in the presence of RA could have been due to increased numbers of B cells at the end of the culture period. Using ^3H -thymidine incorporation, the cultures with RA showed a 43% decrease in proliferation. Since increased proliferation (numbers) of lymphoblastoid B cells was not responsible for the increased amounts of Ig in the supernatant fluids, we examined whether cytokines secreted by

these EBV-trans-formed B cells could be acting as an autocrine factor in increasing Ig synthesis. Two such cytokines would be inter-

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leukin (IL)-1 and IL-6. The latter, in particular, has been demonstrated to be constitutively produced by EBV-transformed B cell lines [7]. EBV-transformed B cell clones were incubated with various concentrations of RA for 6 days. Ig synthesis and the levels of IL-1 and IL-6 were measured by ELISA (R&D Systems) in the culture supernatant fluids. No differences could be detected in IL-1 between the cultures with and without RA. However, the cultures with RA showed a 7- to 91-fold increase in IL-6. These experiments suggest that the direct effect of RA on B cells may be mediated by the secretion of IL-6. We also examined whether RA could modulate steady-state IL-6 mRNA expression. RA (1×10^{-7} M) induced a 4-fold (by densitometry) increase in steady-state IL-6 mRNA at 72 h in an EBV-transformed B cell line. There was no change in the expression of transforming growth factor- β mRNA, and even a decrease in the expression of tumor necrosis factor- α mRNA with the addition of RA. These studies suggest that the enhancing effects of RA on Ig synthesis are mediated, at least in part, by the production of IL-6, perhaps as part of an autocrine pathway.

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