The secretory immunoglobulin A (IgA) antibody response to infections of mucosal surfaces requires transport of IgA from the basal to apical surface of mucosal epithelial cells by a specific transport protein, the polymeric immunoglobulin receptor (pIgR). We have tested the hypothesis that the vitamin A metabolite all-trans retinoic acid (RA) is required for the regulation of pIgR expression by the cytokines interleukin-4 (IL-4) and interferon-g (IFN-g) in HT-29 cells, a well-differentiated human epithelial cell line derived from a colonic carcinoma. pIgR expression is upregulated by IFN-g and IL-4 when HT-29 cells are grown in normal media, but this upregulation was significantly lower when cells were grown in vitamin A-depleted media. Treatment with RA at concentrations from 1009 to 1005 mol/L restored normal levels of pIgR expression. The percentages of cells expressing cellsurface pIgR after 24, 48 and 72 h of treatment with RA, IL-4 and IFN-g were 66 ± 10, 90 ± 5 and 92 ± 1, respectively, significantly higher than the percentages seen without RA treatment, which were 32 ± 2.3, 72 ± 1.2 and 30 ± 7, respectively. In addition, the intensity of fluorescence of pIgR-positive cells was significantly higher in the RA-treated cultures than in the cultures without RA treatment. Similarly, pIgR mRNA levels (adjusted for b-actin mRNA levels) in RA-supplemented cultures were 404, 105 and 949% higher at 24, 48 and 72 h, respectively, than were pIgR mRNA levels in identical cultures grown in the absence of RA. These data indicate that RA strongly interacts with IL-4 and IFN-g to regulate pIgR expression in HT-29 cells, suggesting that vitamin A may be required for proper in vivo regulation of IgA transport in response to mucosal infections.