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Human follicular dendritic cells promote the APC capability of B cells by enhancing CD86 expression levels

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ABSTRACT

Follicular dendritic cells (FDCs) are an essential cellular component of the germinal center (GC) and are believed to exert regulatory effects on the various stages of GC reactions. According to our previous reports, human FDCs express prostacyclin synthase, and prostacyclin analogues augment adhesion and co-stimulatory molecules on the surface of activated B cells. These findings prompted us to investigate whether FDCs would contribute to the antigen-presenting capability of B cells by using the well-established FDC-like cells, HK cells, and tonsillar B cells. Our results show that HK cells significantly enhance the expression levels of CD54, CD80, and CD86 on the surface of activated B cells. The enhancing effect of HK cells on CD86 is impeded by indomethacin and an EP4 antagonist, implying that a certain prostaglandin is mediating the up-regulation. Prostacyclin indeed recapitulates the enhancing effect on CD86, which is inhibited by EP4 as well as IP antagonists. B cells co-cultured with HK cells exhibit an augmented APC activity, which is inhibited by CD86 neutralization. These results reveal another unrecognized function of human FDC.

1. Introduction

Human follicular dendritic cells (FDCs) are an essential cellular component of the germinal center (GC) where B cells undergo massive proliferation and apoptosis, somatic hypermutation, positive selection, isotype switching, and differentiation into memory cells or long-lived plasma cells. In the course of these cellular events, FDCs are believed to play important roles through direct cell-to-cell contacts and by providing diffusible molecules. FDCs induce resting B cells to be responsive to chemotactic signals [1], protect GC B cells from the apoptosis by switching off pre-existing endonucleases [2], and enhance the proliferation and differentiation of activated B cells [3,4]. However, the FDC molecules responsible for those recognized functions are poorly identified, in part, due to the practical difficulty in obtaining pure FDCs in sufficient numbers and lack of proper experimental models. We have successfully established a method of isolating FDC-like primary culture cells, HK cells, from tonsil specimens [5]. Using HK cells, we are studying the molecular mechanisms of FDC–B cell interactions.

It is well known that activated B cells are comparable to dendritic cells in their antigen-presenting abilities. T cells are the second major cellular population of the GC, constituting approximately 10% of total cells [6]. In our previous reports, we demonstrated that human FDCs *in situ* and *in vitro* exhibit a strong expression of prostacyclin synthase [7] and that prostacyclin analogues up-regulate CD54 and CD86 expression levels on activated B cells, leading to a significant enhancement of their APC capability [8]. Based upon these results, we reasoned that human FDCs would promote the expression of co-stimulatory molecules of B cells and contribute to the APC activity in the GC. To test this idea, we performed co-cultures of HK cells and B cells. Our results reveal another aspect of FDC–B cell collaboration.

2. Materials and methods

2.1. Antibodies and other reagents

All the protocols were approved by the ethics committee of Kangwon National University. Anti-IgM (DA4.4, IgG1) and anti-CD40 (G28.5, IgG1) antibodies were obtained from the American Type Culture Collection (ATCC). IL-2 was obtained from Hoffmann-La Roche. Recombinant IL-4 and IL-10 were prepared in our laboratory [9]. Fluorescein isothiocyanate (FITC)-conjugated

Abbreviations: APC, antigen-presenting cell; FDC, follicular dendritic cell; GC, germinal center.

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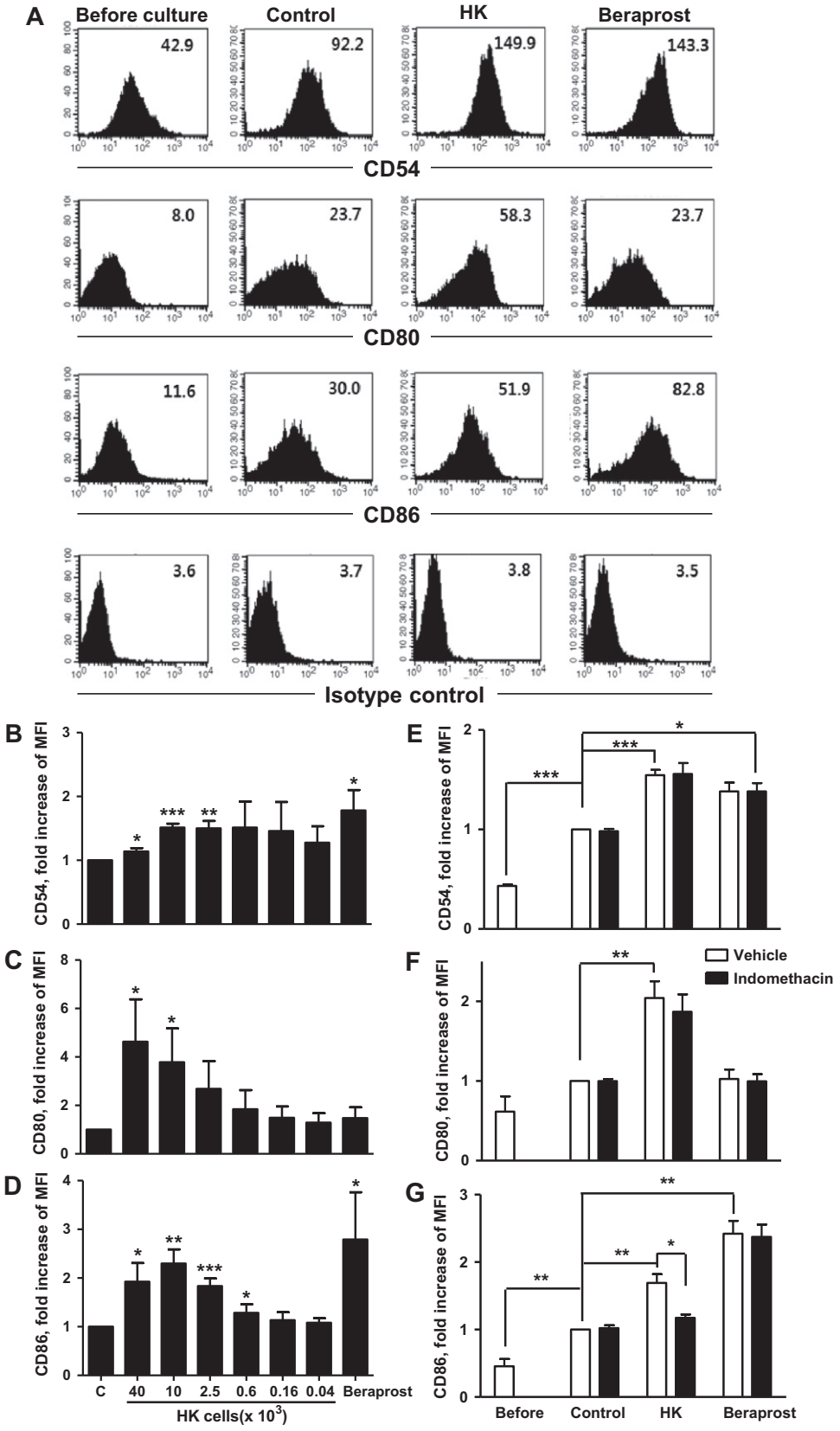

Fig. 1. HK cells enhance expression levels of adhesion and costimulatory molecules on the surface of B cells. Human tonsillar mid-density B cells (1×10^6 cells) were stimulated with anti-IgM, anti-CD40, IL-2, IL-4, and IL-10 in the presence or absence of HK cells {1×10^4 cells (A, E–G) or indicated numbers (B–D)}, indomethacin (10^{-5} M), or beraprost (10^{-6} M) for 72 h. The expression levels of CD54, CD80, and CD86 on B cells before and after cultures were measured after setting up a flowcytometer with isotype-matched control antibodies as shown in representative results (A). The numbers in each histogram indicate the mean fluorescence intensity (MFI) levels of each molecule. Changes of MFIs relative to those of vehicle-treated B cells are presented. Means ± SEM of three independent experiments are depicted. An asterisk(s) indicates a significant difference (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$). C, control B cells cultured without HK cells or beraprost.