Cytokine 102 (2018) 206–210

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Aberrant frequency of IL-35 producing B cells in colorectal cancer patients

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ARTICLE INFO

Keywords:
Colorectal cancer
IL-35 producing B cells

ABSTRACT

Background: The IL-10 dependent regulatory function of B cells had recently more and more investigated and play important roles in cancer immunity, however, beyond IL-10 whether other inhibitory cytokines play an important role in cancer is lacking. Here, we investigated the role of IL-35 producing B cells in colorectal cancer (CRC).

Methods: Thirty-two healthy controls (HC) and 49 untreated CRC patients were enrolled and the IL-35 producing B cells in the peripheral blood were investigated. Additionally, $CD4^+CD25^{+/high}CD127^{low/-}$ regulatory T (Treg) and $CD14^+HLA\text{-}DR^{low/-}$ myeloid-derived suppressor cells (MDSCs) were also investigated.

Results: Results show that IL-35 producing B cells were significantly upregulated during the clinical progression of CRC, and negatively correlated with $CD3^+$ T cell, positively correlated with the frequency of $CD4^+CD25^{+/high}CD127^{low/-}$ Treg cells and $CD14^+HLA\text{-}DR^{low/-}$ MDSCs of these CRC patients.

Conclusions: Together, IL-35 producing B cells were significantly elevated in CRC, indicating this B cell subset might participate in the immune suppression of CRC.

1. Introduction

Colorectal cancer (CRC) is the second most common cause of cancer death among cancers that affect both men and women [1]. Nowadays, advances in understanding of the immune microenvironment have highlighted the role of immunosuppressive T cell, myeloid, dendritic and monocytic sub-populations in inhibition of the anti-tumor immune response. The role of B cells in modulating the immune response to solid tumors is less well understood. On the one hand, B lymphocytes can inhibit tumor development through antibody production and antigen presentation. On the other hand, B lymphocytes have tumor-promoting functions [2,3].

Recently, B cell regulation has been widely studied in both autoimmune and inflammatory diseases, collectively called regulatory B cells (Breg) [4,5]. However, no definitive phenotype has emerged for B cells with regulatory potential, and the exact pathways of Bregs-mediated T cell suppression had not been revealed yet [6]. This has made their study challenging and thus unique B cell regulatory mechanisms have emerged in a disease-dependent manner. Human Breg cell types include $CD27^+CD24^{hi}$ B10 cells, $CD24^{hi}CD38^{hi}$ immature transitional B cells and $CD73^-CD25^+CD71^+$BR1 cells. Nonetheless, a new wave of research is beginning to shed light on the possible roles of Bregs in cancer [5,6]. Among these studies, the immunosuppressive capacity of Breg cells which is often mediated through IL-10 secretion [7]. However, B cells can exert regulatory functions independently of IL-10 production, the IL-35 and TGF-β have also been associated with B cell-mediated immunosuppression [8,9].

IL-35 (p35/Ebi3), belong to the IL-12 family member, characterized by heterodimeric members formed from chain sharing interactions of alpha chains (p35), and beta chains (Ebi3), which is predominantly secreted by regulatory T cells, has been shown to suppress T-cell proliferation and function in a number of *in vitro* and *in vivo* disease models, and appears to be required for suppressor function of mouse and human Tregs [2]. As recently reported, it can also be produced by regulatory B cells in mice [9,10]. However, the IL-35 producing B cells in human studies is lacking [4,11].

Abbreviations: CRC, colorectal cancer; Breg, regulatory B cells; Treg cells, regulatory T cells; MDSCs, myeloid-derived suppressor cells

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http://dx.doi.org/10.1016/j.cyto.2017.10.011
Received 3 August 2017; Received in revised form 24 September 2017; Accepted 11 October 2017

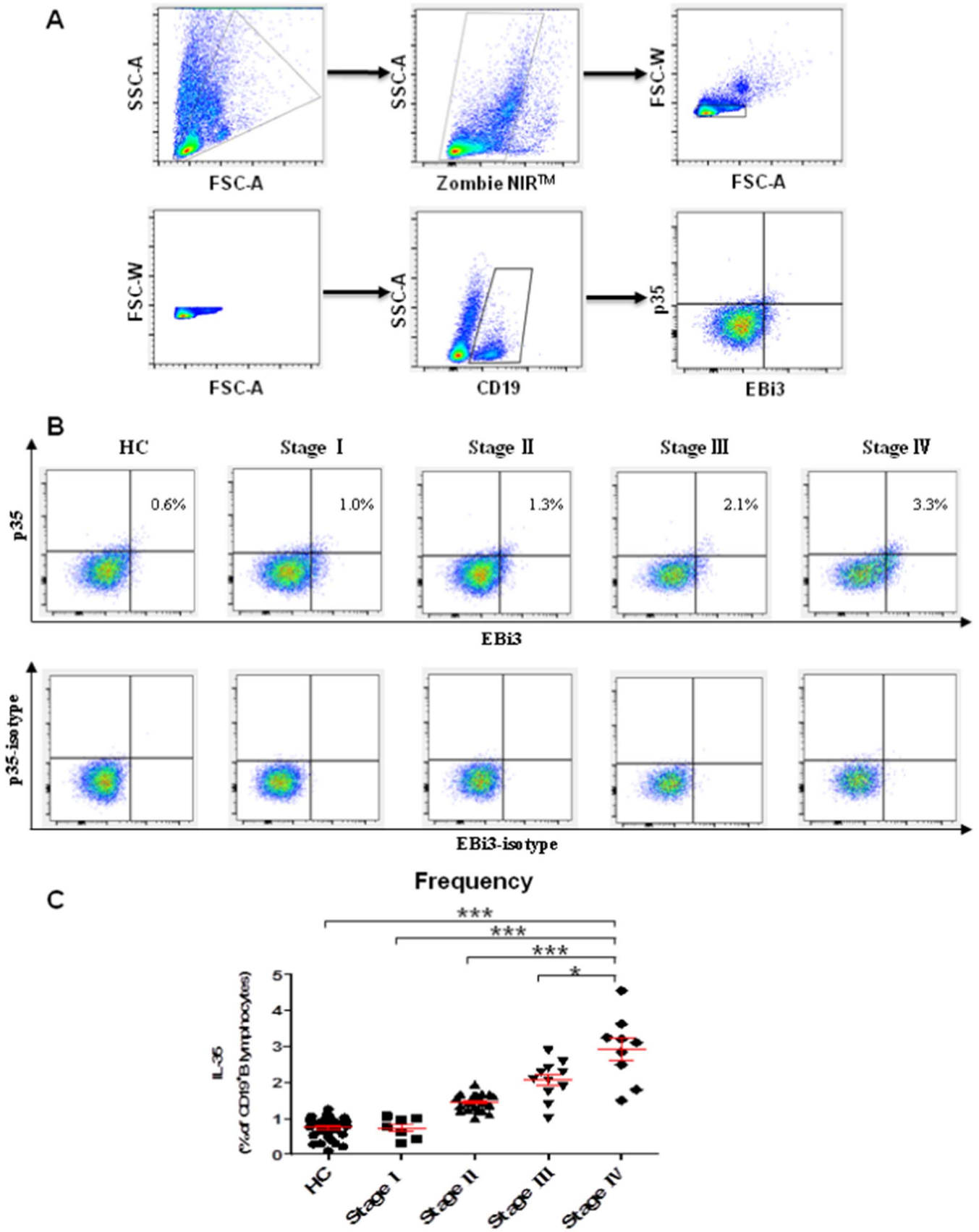

Fig. 1. IL-35 producing B cells were significantly expanded in CRC patients. (A) Gating criteria from the peripheral blood for the live $CD19^+$ B cells and IL-35 producing B cells of CRC patients are shown. (B) Representative data depicting IL-35 producing B cells in HC and different stage CRC patients are shown with isotype. (C) Frequency of IL-35 producing B cells in $CD19^+$ B cells of the stage IV CRC patients (2.93 ± 0.92, n = 9) was significantly elevated compare to HC (0.74 ± 0.29, n = 32, $p = .0002$), stage I (0.73 ± 0.30, n = 7, $p = .0022$), stage II (1.45 ± 0.23, n = 22, $p = .0002$) and stage III (2.06 ± 0.54, n = 11, $p = .0015$). The p value was calculated by means of Mann-Whitney U Test. $^{**}p < .01$, and $^{***}p < .001$.