Heparin-Binding EGF-Like Growth Factor Modulates the Bidirectional Activation of CD4$^+$ T Cells and Dendritic Cells Independently of the Epidermal Growth Factor Receptor

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Background: Allergic asthma results from the improper activation of adaptive immunity. Some of its pathological features have been linked to the epidermal growth factor receptor (EGFR) and its ligands, such as heparin-binding EGF-like growth factor (HB-EGF). Although some EGFR ligands and EGFR have been implicated in immune function, the effect of HB-EGF on the adaptive arm remains unclear. We sought to examine the role of HB-EGF in the function of dendritic cells (DCs) and CD4$^+$ T cells. We hypothesized that HB-EGF promotes the activation of DCs and CD4$^+$ T cells. Methods: Splenic CD4$^+$ T cells were isolated and purified from ovalbumin (OVA) specific TCR transgenic DO11.10 mice. Mouse bone marrow-derived DCs (BMDCs) were loaded with OVA and co-cultured directly with CD4$^+$ T cells or separated by Transwell inserts. Cells were treated with either HB-EGF neutralizing antibody or afatinib, a covalent EGFR inhibitor, for 24 h. BMDCs were also treated in isolation with recombinant HB-EGF (rHB-EGF) for 24 h. Gene expression was assessed at the mRNA and protein levels by qPCR and flow cytometry. Membrane-bound HB-EGF localization was assessed following BMDC-CD4$^+$ T cell co-culture for 12 h via confocal microscopy. Results: Both BMDCs and CD4$^+$ T cells express HB-EGF. HB-EGF neutralization but not EGFR inhibition in co-culture reduced cell-surface expression of activation markers CD69 in CD4$^+$ T cells and CD86 and MHC class II in BMDCs. Expression of activation markers was unchanged in co-cultured CD4$^+$ T cells and BMDCs separated by Transwell inserts following treatment with HB-EGF neutralizing antibody. rHB-EGF did not alter BMDC expression of activation markers CD25, CD86, MHC class II, and chemokine (C-C motif) receptor 7; CD4$^+$ T cell polarizing cytokines interleukin (IL) 4, IL-6, IL-12 subunit beta, and interferon-γ; and transcription factors T-bet and GATA3. Membrane-bound HB-EGF co-localized with CD3 and F-actin at DC-CD4$^+$ T cell contact sites. Conclusions: HB-EGF promotes the activation of CD4$^+$ T cells and BMDCs in a contact-dependent fashion independently of EGFR. Soluble HB-EGF alone is insufficient to activate DCs. HB-EGF is localized at the immunological synapse between DCs and CD4$^+$ T cells. These results suggest that HB-EGF plays a role in the early activation of dendritic cells and CD4$^+$ T cells through interactions at the cell surface. This abstract is funded by: CIHR and the Richard and Edith Strauss Foundation

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