ANB032 is a novel BTLA/HVEM Checkpoint Modulator for Autoimmune/Inflammatory Disease

Abstract

BTLA was first identified as a negative immune regulator on T cells and B cells, most closely related to PD-1 and CTLA-4. In contrast to other inhibitory receptors whose expression is induced after cell activation, BTLA is constitutively expressed on many immune cells (Sedik et al., 2003; Waterboom et al., 2003). BTLA expression levels vary substantially among different lymphoid and non-lymphoid cell types (Yasui et al., 2004; Huchko et al., 2005). The ligand of BTLA is Herpes-Virus entry mediator (HVEM). In the past decade, HVEM has emerged as a major and complex co-inhibitory signaling molecule. In addition to binding to BTLA, HVEM also serves as a receptor for four other ligands: LIGHT, lymphotoxin β (LTβ), glycoprotein D (GpD) (Spier et al., 2004; Murphy et al., 2006), and CD40L (Caillot et al., 2004; Del Rio et al., 2010).

Engagement of BTLA by HVEM in trans across two cells induces Tph phosphorylation of the ITIM motifs in BTLA, allowing the recruitment of the SHP-1 and SHP-2 phosphotyrosine kinases (Stark et al., 2000; Vardoni et al., 2004). Recruitment of SHIP and SHIP2 results in the attenuation of T cell proliferation, growth and cytokine production for T cell expansion (Stein et al., 2004; Morel et al., 2001). HVEM and BTLA interactions can also occur in cis on the same cell, resulting in BTLA-mediated silencing of co-stimulatory signals through HD exchange. The elucidation of this cis complex is thought to be one of the mechanisms by which BTLA regulates HVEM co-inhibition.

The complexity of the BTLA/HVEM network makes therapeutic inhibition strategies more challenging than for other inhibitory molecules or receptors. Thus, BTLA is emerging as a unique immune checkpoint receptor and targeted therapeutic agent in cancer and autoimmunity. We report an anti-human BTLA antibody designated ANB032 that modulates the BTLA/HVEM trans/intracellular signaling pathways via three potential mechanisms: 1) ANB032 does not compete with BTLA/HVEM interactions and thus does not prevent HVEM-mediated trans inhibitory signaling through BTLA. However, binding of ANB032 does inhibit HVEM-mediated cis-inhibitory signaling. 2) ANB032 permits BTLA/HVEM cis complex formation, inhibiting co-inhibitory signaling mediated through HVEM ligands. 3) ANB032 has the capacity to directly induce inhibitory signaling through HVEM binding, which is potentiated by Fc receptor engagement. Via these mechanisms, ANB032 interactions to down-modulate T cell responses have the potential to restore and maintain immune balance in autoimmune and inflammatory diseases.