



The Roles of IL-6 Amplifier in Autoimmune Diseases

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ABSTRACT

We have shown that interaction between non-immune tissues and immune system plays important roles in autoimmune diseases (Hirano, Proc. Japn. Acad., Ser. B, 2010, Sawa et al., J. Exp. Med., 2006). IL-17A together with IL-6 induces the NF κ B-triggered positive feedback loop for IL-6 signaling in type 1 collagen+ non-immune cells (IL-6 amplifier) through the simultaneous activation of NF κ B and STAT3. The IL-6 amplifier plays roles in F759 arthritis and EAE (Ogura et al., Immunity 2008). We have proposed a Four Step Model for MHC class II associated autoimmune disease: 1) T cell activation regardless of antigen specificity; 2) tissue-specific accumulation of activated T cells; 3) transient activation of the IL-6 amplifier; and 4) local events capable of inducing continuous activation of the IL-6 amplifier. The interaction of these events results in the chronic activation of IL-6 amplifier leading to the manifestation of autoimmune diseases and chronic inflammatory proliferative diseases (Murakami et al., J. Exp. Med. 2011, Murakami and Hirano, Front. Immunol., 2011). Moreover, we have recently shown that regional neural activation is one of local events capable of activating the IL-6 amplifier in the region, giving rise to establish a gateway for autoreactive CD4⁺T cells to pass the blood-brain barrier (Arima et al., Cell 2012). Accumulating evidences continue to suggest that the IL-6-amplifier activation is indeed associated with various human diseases and that the identified genes may make for potential therapeutic targets.