

## SUMMARY OF Ph.D. DISSERTATION

School Fundamental Science and Technology	Student Identification Number	SURNAME, First name SUZUKI, Eriko
<p>Title</p> <p>Suppression of natural immune and leukemia cell functions by NF-<math>\kappa</math>B inhibitors</p>		
<p>Abstract</p> <p>Recently, it has been demonstrated that excess activation of macrophages and mast cells are strongly involved in the pathogenesis of inflammation and cancer. In the present study, I have investigated the effect of an NF-<math>\kappa</math>B inhibitor, DHMEQ, on the regulation of macrophages and mast cells activations, and involvement of NF-<math>\kappa</math>B in the regulation of these cells. Further, I have examined the mechanisms of rituximab, a chimeric antibody for CD20,-mediated chemosensitization in B cell non-Hodgkin's lymphoma cells. The mechanisms of macrophage activation and NF-<math>\kappa</math>B activation, and the structure and functions of rituximab were described in the 1<sup>st</sup> chapter as an introduction.</p> <p>In the 2<sup>nd</sup> chapter, inhibitory effect of DHMEQ on lipopolysaccharide (LPS)-induced cytokine secretions such as IL-6, 12, TNF-<math>\alpha</math>, iNOS, COX-2 expressions and phagocytosis were examined in RAW264.7 cells. As a result, DHMEQ inhibited the expressions and secretions of these inflammatory mediators described above, at the concentration that has no cytotoxicity. Moreover, DHMEQ inhibited LPS-induced phagocytosis of <i>E.coli</i>, suggesting that NF-<math>\kappa</math>B pathway is involved in the mechanism of macrophage phagocytosis.</p> <p>In the 3<sup>rd</sup> chapter, I focused on mast cell-derived LTs productions, and investigated the mechanism of DHMEQ-mediated inhibition of LTs production in rat basophilic leukemia cell line, RBL-2H3 cells. In RBL-2H3 cells, IgE/DNP-induced NF-<math>\kappa</math>B activation and LTs productions were inhibited by (-)-DHMEQ. Since five lipoxygenase (5-LO), and 5-LO activating protein (FLAP) are both essential and key enzymes required for LTs synthesis, the effect of DHMEQ on the expressions of these enzymes was first examined. As a result, DHMEQ strongly inhibited the expressions of both proteins while there is no inhibition on the enzymatic activities. In innate immune cells, it has been known that complex formation of Bcl-10, Malt1 and CARMA1 (CBM complex) is critical for NF-<math>\kappa</math>B activation. Interestingly, treatment of RBL-2H3 cells with DHMEQ resulted in dissociation of the complex formation, which is likely due to the inhibition of CARMA1 expression. The inhibition of CBM complex may be a positive feedback mechanism which leads to suppression of the NF-<math>\kappa</math>B pathway.</p> <p>In the 4<sup>th</sup> chapter, I have examined the mechanism of CD20 monoclonal antibody, rituximab-mediated chemosensitization in B-NHL cells. It has been reported that the NF-<math>\kappa</math>B pathway is involved in the mechanism of the drug resistance. The present study using Ramos B-NHL cells and Ramos RR1 (rituximab-resistant) cells demonstrated that the Akt survival pathway plays an critical role in drug resistance and rituximab-resistance. Moreover, treatment of Ramos cells with rituximab resulted in inhibition of the Akt and the NF-<math>\kappa</math>B survival pathway, and the expression of anti-apoptotic molecule, Bcl-xL.</p> <p>In conclusion, it was demonstrated using DHMEQ that NF-<math>\kappa</math>B is directly involved in the activations of innate immune cells. Inhibition of innate immune cell functions will lead to anti-inflammatory and anti-cancer effect. Moreover, I have demonstrated for the first time that rituximab sensitized lymphoma cells to anti-cancer drug-induced apoptosis, in which the Akt and the NF-<math>\kappa</math>B pathways are involved.</p>		