Chapter 6: Conclusions

CD44 is a widely distributed cell surface glycoprotein whose principal ligand has been identified as hyaluronic acid (HA), a major component of the extracellular matrix (ECM). We have shown for the first time that interaction between HA and CD44 can regulate murine B cell effector functions and that these interactions may play a critical role during normal or autoimmune responsiveness of B cells.

Inasmuch as, CD44 also plays a major role in the lymphocyte adhesion to the endothelial cells, dysregulation in the interaction between activated cytotoxic lymphocytes expressing CD44 and endothelial cells bearing the appropriate ligand such as the hyaluronate, could lead to endothelial cell lysis. Furthermore, endothelial cell injury could lead to the pathogenesis associated with a variety of clinical diseases. Our studies demonstrated that perforin KO mice had decreased levels of VLS in the lung, liver and spleen and *gld* mice had decreased levels of VLS in the liver and spleen (Rafi et al., 1998). This demonstrated for the first time that these cytolytic/apoptotic molecules are directly involved in vascular leak. This also suggested that VLS may result from active damage to the endothelial cells.

We also showed that CD44 is directly involved in the injury to the endothelial cells caused by CTL and LAK cells, during IL-2-induced VLS. We observed markedly diminished VLS following IL-2-treatment in CD44 knockout (KO) mice. Our data suggests that blocking CD44 helps in reducing the IL-2-induced VLS and therefore such an approach may serve as a useful tool to prevent endothelial cell damage seen in a variety of clinical disorders.

The TCR-independent CD44-mediated cytotoxicity by CTL/NK cells may represent a double-edged sword. On the one hand, it may play a beneficial role by killing virally infected or cancer cells that downregulate MHC or resist TCR-mediated lysis. On the other hand, such non-specific killing may account for

tissue injury particularly at sites of chronic inflammation. The current study also demonstrates that blocking CD44 may serve as a novel and useful therapeutic tool to prevent the endothelial cell damage seen in a variety of clinical disorders.