GENETICS AND FUNCTIONS OF INNATE-LIKE LYMPHOCYTE SUBSETS

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I Julia Rolf, Vinicius Motta, Nadia Duarte, Marie Lundholm, Emma Berntman, Marie-Louise Bergman, Lydia Sorokin, Susanna L. Cardell and Dan Holmberg. (2005). The enlarged population of marginal zone/CD1d(high) B lymphocytes in nonobese diabetic mice maps to diabetes susceptibility region Idd11. J Immunol. *174*, 4821-7.

II Julia Rolf, Emma Berntman, Martin Stenström, Emma Smith, Robert Månsson, Hanna Stenstad, Tetsuya Yamagata, William Agace, Mikael Sigvardsson and Susanna L. Cardell. (2007). Molecular profiling reveals distinct functional attributes of CD1d-restricted natural killer (NK) T cell subsets. *Submitted manuscript*.

III Emma Berntman, Julia Rolf, Cecilia Johansson, Per Andersson and Susanna L. Cardell. (2005). The role of CD1d-restricted NK T lymphocytes in the immune response to oral infection with *Salmonella typhimurium*. Eur J Immunol. *35*, 2100-9.

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The immune system contains three different branches: innate immunity, adaptive immunity and innate-like lymphocytes that share properties both with the innate and adaptive immune cells. The innate-like lymphocytes have the capacity to rapidly become activated by invading pathogens and also to modulate immune responses and thereby inhibit or promote inflammation. However, understanding of the innate-like lymphocyte properties and functions has remained incomplete. This thesis describes the properties, genetic regulation, gene-expression profile and functional response of innate-like lymphocyte populations in mice.

To determine the role of the innate-like B lymphocyte subset called marginal zone (MZ) B cells in autoimmunity this population was studied in the nonobese diabetic (NOD) mouse model of autoimmune diabetes. The MZ B cell population size was expanded compared to the non-autoimmune C57Bl/6 mice. The increase in MZ B cell numbers occurred before autoimmunity was initiated and not as a secondary consequence of diabetes. The MZ B cell population in NOD mice was genetically most strongly associated with diabetes-susceptibility loci Idd9/11 on chromosome 4. In addition to MZ B cells, the innate-like lymphocyte population termed natural killer T (NKT) cells was studied. NKT cells possess potent immunomodulatory functions and are divided into two subsets based on the TCR usage. Microarray technology was utilized for analyzing the global gene expression profile of the two NKT cell subsets in comparison to conventional $CD4^+$ T cells. The NKT cells over-expressed genes encoding NK cell receptors, pro-cytotoxic molecules and chemokine-receptors that promote homing to inflamed tissues. Expression of transcription factors associated with immune cell development, such as Hhex and Id2 was induced already during thymic development. The microarray analysis of the NKT cell subsets has provided profound new insights into their features, transcriptional regulation and potential functions. The functional role of NKT cells in infectious disease was studied during infection by the pathogenic bacteria *Salmonella typhimurium*. The NKT cells became strongly activated by the ongoing *Salmonella* infection and participated in fighting *Salmonella* during the early phase of the infection through production of IFN-γ. Activation of NKT cells via infection caused by an intracellular pathogen strongly skewed the NKT cells towards IFN-γ dominated immunity.

This thesis explores the properties of innate-like lymphocyte populations, with emphasize on the underlying genetic regulation and global gene expression profile. In addition, the functional role of the NKT cells in the immune response against infection is described.

Keywords: innate-like lymphocyte, CD1d, autoimmunity, genetic mapping, microarray, *Salmonella* infection

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