学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

Study on the regulation of $CD8^+$ T cell immune response through nuclear receptor RORα and REV-ERB

（核内受容体 RORα および REV-ERB を介した $CD8^+$ T 細胞免疫応答の制御に関する研究）

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$CD8^+$ T cells are crucial for the body protection against intracellular pathogens and tumors. There is a growing interest in pharmacologically manipulating the quality of $CD8^+$ T cell response to develop better vaccination and immune therapies. Nuclear receptors RORα and REV-ERB are a set of ligand-dependent transcription factors generally known to regulate circadian rhythm and metabolism in multiple organs. Recent advances in the development of synthetic ligands for these nuclear receptors provide the opportunity of targeting them in various diseases. The roles of RORα and REV-ERB in the immune system have not been sufficiently characterized. In this study, the roles of RORα and REV-ERB in the regulation of $CD8^+$ T cell immune responses and the potential of their specific ligands for clinical application were examined.

Chapter I demonstrated that RORα activation by an agonist treatment impairs the proliferation and survival of activated $CD8^+$ T cells *in vitro* through the downregulation of genes associated with cholesterol biosynthesis. RORα deficiency resulted in the increase in both frequency and absolute number of memory precursor effector $CD8^+$ T cells after infection. The results indicate that RORα limits the expansion of T cells during immune response by promoting the death of activated $CD8^+$ T cells.

In chapter II, the treatment of mice with a REV-ERB agonist after infection was shown to skew memory $CD8^+$ T cells toward effector-like lineage bearing strong cytotoxic function. The agonist injection improved the protective immunity against re-infection. These results suggest a novel strategy to pharmacologically manipulate the T cell immune response and to improve the efficacy and the safety of vaccines.

Taken together, in this thesis, targeting RORα and REV-ERB by synthetic agonists in antigen-responding $CD8^+$ T cells was shown to drastically alter the cell fate including the survival and functional differentiation. The finding in this study provide insights into the development of immunotherapies targeting the nuclear receptors in $CD8^+$ T cells.