学位論文抄録

Downregulation of 15-PGDH enhances MASH-HCC development via fatty acid-induced T-cell exhaustion

（15-PGDH の下方制御は脂肪酸代謝の機能不全による T 細胞の枯渇を通じて MASH-HCC の発生を促進する）

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Abstract of the Thesis

Background and Aims: Hepatocellular carcinoma (HCC) mainly develops from chronic hepatitis. Metabolic dysfunction-associated steatohepatitis (MASH) has gradually become the main pathogenic factor for HCC due to the rising incidence of obesity and metabolic diseases. 15-Hydroxyprostaglandin dehydrogenase (15-PGDH) is the enzyme that degrades prostaglandin 2 (PGE2), which is known to exacerbate inflammatory responses. However, the role of PGE2 accumulation caused by 15-PGDH downregulation in the development of MASH-HCC has not been determined.

Methods: We utilized the steric animal model (STAM) to establish a MASH-HCC model using WT and 15-Pgdh+/− mice to assess the significance of PGE2 accumulation in MASH-HCC development. Additionally, we analyzed clinical samples obtained from MASH-HCC patients.

Results: We showed that PGE2 accumulation in the tumor microenvironment (TME) induced ROS production in macrophages and the expression of cell growth-related genes and antiapoptotic genes. On the other hand, the downregulation of fatty acid metabolism in the background liver promoted lipid accumulation in the TME, causing a decrease in mitochondrial membrane potential and CD8+ T-cell exhaustion, which led to enhanced MASH-HCC development.

Conclusions: 15-PGDH downregulation inactivates immune surveillance by promoting the proliferation of exhausted effector T cells, which enhances hepatocyte survival and proliferation and leads to MASH-HCC development.