

博士論文(要約)

Effects of H3K27 Demethylase Inhibitor on Renal Fibrosis.

(H3K27 脱メチル化酵素阻害薬の腎線維化に与える影響)

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論文の内容の要旨

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The onset and progression of chronic kidney disease (CKD) are provoked by renal interstitial fibrosis. Many mechanisms have been proposed, but definite treatment has still been undiscovered.

In this study, I evaluated the anti-fibrotic and protective effects of GSKJ4 on the kidney, which is one of the histone demethylase inhibitors that are recently highlighted in a wide range of fields.

In *in vitro* study, I stimulated normal rat kidney interstitial fibroblast cells (NRK49F) with transforming growth factor-beta (TGF- β) to induce pro-fibrotic changes. During TGF- β stimulation, NRK49F cells were treated with GSKJ4, and gene expression changes were measured. In NRK49F cells treated with TGF- β , GSKJ4 inhibited fibrosis-related genes.

To elucidate the exact molecular mechanism of the protective effect of GSKJ4, RNA-seq analysis was performed in the NRK49F cells treated with or without GSKJ4. In KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis, fibrosis-related pathways were enriched significantly, which also shows fibrosis-related genes are candidate genes suppressed by GSKJ4 during fibrotic changes.

Meanwhile, I performed *in vivo* study by using the mice with unilateral ureter obstruction (UUO), a kidney fibrosis model. The UUO mice with or without intraperitoneal GSKJ4 treatment were evaluated by areas of kidney fibrosis and fibrosis-related gene expression changes. The results showed that the areas of kidney fibrosis and the pro-fibrotic gene expression levels did not show statistically significant differences by GSKJ4 treatment. Based on my *in vitro* experiments, I concluded that GSKJ4 could ameliorate fibrosis-related pathways, but my *in vivo* research failed to show the anti-fibrotic effect of GSKJ4. Further research needs to verify the effect of GSKJ4 on kidney fibrosis.