PKR 下流の分子を標的とした新たな肝細胞癌治療法の開発

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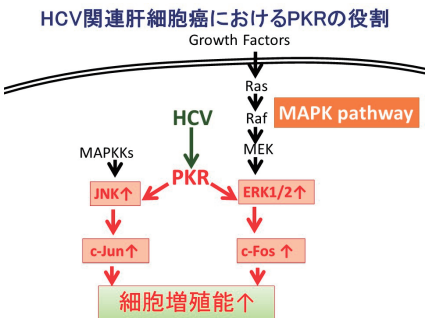
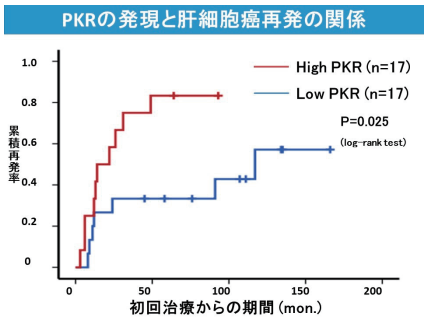
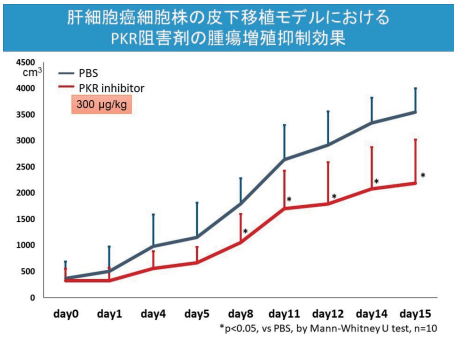
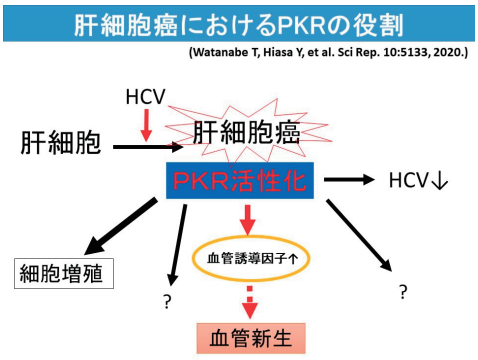
プロジェクト概要

肝細胞癌は慢性肝炎･肝硬変から発生するため、死亡者数の多い予後不良な疾患である。我々はProtein kinase R (PKR)が、肝細胞癌において非癌部の肝組織に比べて強発現していることを同定し,また肝細胞癌においてPKRはERK1/2, JNKのシグナルを介してc-Fos, c-Junを活性化し、それにより細胞増殖促進作用を示すことを見出した。

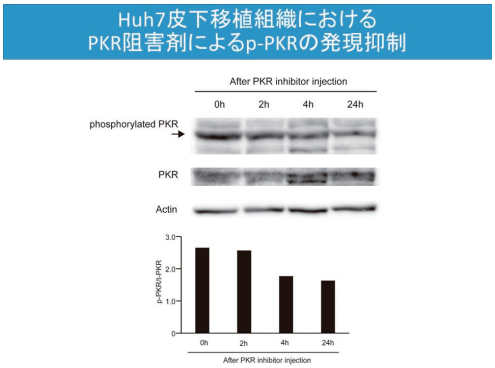








PKR阻害剤 (imidazolo-oxiindole)投与による腫瘍の増殖抑制効果を*in vivo*モデルで証明。さらに血管新生を抑制することで肝細胞癌の微小環境にも影響することを示した。その機序としてPKR阻害剤はVEGF-A, VEGF-B, PDGF-A,PDGF-Bなど複数の増殖因子の発現を抑制することも明らかとした。



既存のPKR阻害剤のPKRシグナル抑制効果は強くない。
PKRの構造上, PKR活性化を阻止できる十分なキャビティ―が存在しない。

PKR下流の分子をターゲットとした阻害剤の探索

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LC-MS/MSによるPKR下流標的分子の網羅的解析

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癌細胞内代謝制御に関与するHexokinase-2などを同定
→PKR, HK2を阻害し、強力に肝細胞癌増殖を抑制する新規化合物の探索

新規化合物のハイスループットなスクリーニング法の確立、化合物ライブラリーの取得が課題。
PKR関連分子の阻害剤として特許出願を目指す。

Development of new therapeutic methods for hepatocellular carcinoma targeting molecules downstream of PKR

Principal Investigator

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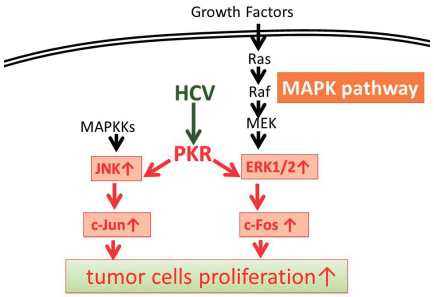
Professor Yoichi HIASA

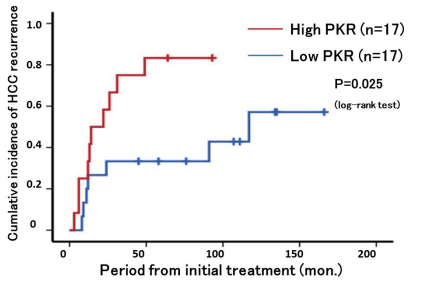
Project Outline

Because hepatocellular carcinoma develops from chronic hepatitis and cirrhosis, it has a high mortality rate and a poor prognosis. We have identified that protein kinase R (PKR) is highly expressed in hepatocellular carcinoma compared with non-cancerous liver tissue, and that PKR activates c-Fos and c-Jun through ERK 1/2 and JNK signals, thereby showing a cell growth-promoting effect in hepatocellular carcinoma.

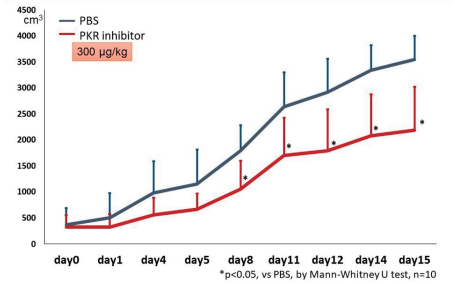
Role of PKR in HCV related hepatocellular carcinoma



The relation between PKR expression and HCC recurrence

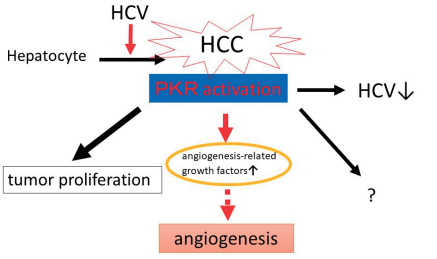


The PKR inhibitor suppressed the growth of HCC in xenograft transplantation experiments (*in vivo* model)



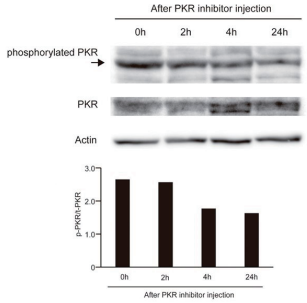
Role of PKR in hepatocellular carcinoma

(Watanabe T, Hiasa Y, et al. Sci Rep. 10:5133, 2020.)



Inhibitory effects of PKR inhibitors (imidazolo-oxidole) on tumor growth were demonstrated in an *in vivo* model. In addition, it was shown that the microenvironment of HCC was also affected by suppressing the angiogenesis. As the mechanism, we also found that PKR inhibitors suppressed the expression of several growth factors, including VEGF-A, VEGF-B, PDGF-A, and PDGF-B.

Suppression of PKR phosphorylation in xenograft tumor



The PKR signal suppression effect of existing inhibitor are not sufficient.
The structure of PKR has no sufficient cavities to prevent PKR activation.

Exploration for new inhibitors targeting molecules downstream of PKR

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Comprehensive analysis of PKR downstream target molecules by **LC-MS/MS**

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Identification of some molecules such as Hexokinase -2 that is concerned with metabolic control in cancer cells.

→Search for new compounds that inhibits PKR and HK2 potently inhibits HCC growth.

Research problems is to obtain a compound libraryand are to establish a high-throughput screening method for that new compounds.
Our aim is acquisition of the patent as an inhibitor of the PKR related molecules.