

科学研究費助成事業 研究成果報告書

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研究課題名(和文) FXR agonistを用いた肝切除後肝再生促進療法の臨床応用を見据えた基礎研究

研究課題名(英文) Clinical implication of Farnesoid-X-receptor agonist in liver regeneration after hepatectomy

研究代表者

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研究成果の概要(和文)：マウス実験に関しては、70%肝切除モデルの確立を行った。B6マウスにおける肝切除の手技的な準備・プロトコール作成は可能であった。並行してヒトサンプル解析を行い、FXR抗体(PPMX社、Clone No. A9033A)を用いて肝切除例の背景肝組織の免疫染色を施行した。良好な染色の局在が得られたものの、染色切片における肝細胞のうち50%以上の核染色(核内移行)が見られる症例はほぼ全例(n>50)であり、これの定量的な評価をFXR活性化群・不活性化群に分けることは困難であった。臨床的な意義を検証するためには他のFXR評価法を確立する必要があると考えられた。

研究成果の概要(英文)：Mouse model of 70% hepatectomy was established. Protocol was prepared for the experiment with FXR agonist. In clinical experiment with paraffin embedded section, immunohistochemistry was performed with FXR antibody (PPMX corp., Clone No. A9033A). Staining pattern was appropriate and nuclear localization of FXR was confirmed. On the other hand, nuclear localization of FXR in more than 50% of hepatocytes in background liver was seen in almost all samples (n>50). Therefore, it was hard to assign them into two groups with/without FXR activation. Other methodology is required for evaluating activation status of FXR in hepatocytes.

研究分野：消化器外科学(特に肝領域)

キーワード：FXR agonist 肝再生 肝切除

1. 研究開始当初の背景

肝切除後、肝組織中 Farnesoid X receptor (FXR)は胆汁酸を ligand として活性化され、FoxM1 を介して肝再生を促進することが報告された (Huang et al. Science 2006)。我々は肝切除後、胆汁酸の外瘻により血清胆汁酸が低下しかつ肝再生が抑制されることを報告した (Otao et al. Br J Surg 2012)。

2. 研究の目的

近年、糖尿病・脂肪性肝炎を代表とする脂質代謝異常疾患の治療薬として注目される FXR agonist が、肝切除後の肝再生を促進するかどうかについて動物モデルを用いて検証する。また、ヒト肝組織サンプルを用いて、背景肝の病理組織学的特徴と FXR-signaling の関連性を包括的に調べる。今研究の解析結果を、臨床試験を展開する上での基盤情報としたい。

3. 研究の方法

マウスモデル解析：FXR agonist (GW4064) 投与時の 2/3 肝切除後の BA-FXR signaling および肝再生を placebo 群と比較する。

ヒトサンプル解析：当科にて肝切除を施行された症例を対象に背景肝組織の BA-FXR signaling を免疫組織化学的に解析し、疾患や病態に応じた特性を明らかにする。

4. 研究成果

マウス実験に関しては、70% 肝切除モデルの確立を行った。B6 マウスにおける肝切除の手技的な準備・プロトコール作成は可能であった。並行してヒトサンプル解析を行い、FXR 抗体 (PPMX 社、Clone No. A9033A) を用いて肝切除例の背景肝組織の免疫染色を施行した。良好な染色の局在が得られたものの、染色切片における肝細胞のうち 50%以上の核染色(核内移行)が見られる症例はほぼ全例 (n > 50) であり、これの定量的な評価を FXR 活性化群・不活性化群に分けることは困難であった。臨床的な意義を検証するためには他の FXR 評価法を確立する必要があると考えられた。

5. 主な発表論文等

(研究代表者、研究分担者及び連携研究者には下線)

[雑誌論文](計 48 件) 全て査読有

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〔学会発表〕(計 3 件)

1. 第 35 回 Microwave Surgery 研究会(2016 年 9 月 16 日 メルパルク熊本・熊本県熊本市)
 岡部弘尚、山下洋市、今井克憲、甲斐田剛圭、石河隆敏、馬場秀夫
 「肝細胞癌切除後再発に対して局所凝固療法を行った症例における予後規定因子の探索」
2. 第 71 回日本消化器外科学会総会(2016 年 7 月 15 日 アスティ徳島・徳島県徳島市)
 岡部弘尚、調 憲、吉住朋晴、内山秀昭、池上徹、播本憲史、伊藤心二、木村光一、馬場秀夫、前原喜彦
 「肝細胞癌の再発形式・生存予後に関する、組織構造分類の新たな提言」
3. 第 116 回日本外科学会定期学術集会(2016 年 4 月 15 日 大阪国際会議場・大阪府大阪市)
 岡部弘尚、調 憲、吉住朋晴、内山秀昭、池上徹、播本憲史、伊藤心二、木村光一、馬場秀夫、前原喜彦
 「肝細胞癌の発育進展と間葉系形質獲得からみた原発性肝癌取り扱い規約の組織構造分類の意義」

〔図書〕(計 0 件)

〔産業財産権〕

出願状況(計 0 件)

名称：
 発明者：
 権利者：
 種類：
 番号：
 出願年月日：
 国内外の別：

取得状況(計 0 件)

名称：
 発明者：
 権利者：
 種類：
 番号：
 取得年月日：
 国内外の別：

〔その他〕
 ホームページ等

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無し