HCV JFH-1 株の感染増殖細胞系を基盤とした、HCV 全生活環を標的とする薬剤スクリーニングを行った。これまでに、Hsp90 阻害剤、エストロゲン受容体モジュレーター、代謝拮抗剤などで強い HCV 増殖阻害作用が観察されている。また、レプリコン細胞で HCV RNA 複製阻害作用のない糖鎖修飾阻害剤の中にも抗 HCV 活性が認められた。従来の抗 HCV 化合物とは異なる作用機序を持つ創薬シーズが見出されるものと期待される。

E．結論

本研究期間に以下の研究成果を得た。

（1）HCV 粒子形成機構の解析

1）HCV 粒子表面の脂質成分が粒子構造保持、感染性に重要であることを示した。

2）HCV 粒子形成の場として油滴が重要な役割を果たしていることを明らかにした。

3）HCV 構造蛋白間、コア蛋白-RNA の結合様式を同定し、粒子アセンブリーモデルを提唱した。

（2）HCV 複製増殖機構の解析

1）NS5A、NS4A、NS5B 蛋白とそれぞれ結合する宿主因子 FKBP8、CKB、CCT5 を同定し、それらを介した HCV RNA 複製調節機序を明らかにした。

2）ゲノム複製効率を規定する RNA シスエレメント、適応変異を同定した。

（3）HCV 病原性発現機構の解析

1）コア蛋白による肝脂肪化、癌化に PA28・、PPAR・、SOCS1 が重要な役割を果たすことを見出した。

2）DDX3, vimentin がコア蛋白と相互作用し HCV 産生に影響を与えること、コア蛋白の一部はミトコンドリアに局在しミトコンドリア蛋白発現に介入することを示した

3）NS3-p53、NS5A-Syk の各相互作用よる p53、Syk の機能抑制機構を明らかにした。

（4）HCV 持続感染機構の解析

1）樹状細胞が抗 HCV CTL を誘導する機構として、傷害破壊された感染細胞由来のウイルス因子が樹状細胞に取り込まれ、TLR3 依存的に NK が誘導され、T 細胞が活性化されるモデルを提唱した。

2）NS3-4A 蛋白は TRIF を切断せず、TRIF を介するシグナル経路を抑制しないことを明らかにした。

（5）HCV 複製増殖細胞系の開発、改良

1）RNA Pol I システムを利用し感染性ウイルス持続産生細胞株を樹立した。

2）ゲノム複製の簡便な定量化アッセイ系及び複製細胞の可視化モデルを開発し Lipid-rich albumin を加えた無血清培地による複製細胞の長期培養法を確立した。

3）遺伝子型 1b/2a キメラウイルスを作製し、また新たに急性肝炎患者血清からクローン化した HCV ゲノムの複製系を作製した。

（6）動物モデルの開発

1）タマリン、マーモセットを用いて急性、慢性肝炎発症のサロゲート動物モデルを樹立した。

2）GBV-B 急性感染系は、HCV と同様に多臓器指向性感染モデルとなることを見出した。

3）ヒト肝臓キメラマウスの改良を目指して肝細胞死誘導 Tg マウスを樹立した。

（6）抗 HCV 薬の探索

1）HCV ゲノム複製阻害化合物として、シクロスポリン誘導体、スタチン剤、コレステロール生合成阻害剤、スフィンゴ脂質生合成阻害剤、ミゾリビン、フラーレン骨格化合物などを見出した。

2）HCV 粒子形成阻害化合物としてグルコシダーゼ阻害剤、スフィンゴ脂質生合成阻害剤を見出した。

F. 健康危険情報

特になし

G. 研究発表

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「研究成果の刊行に関する一覧表」に記載した。

H. 知的財産権の出願・登録状況

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Ⅱ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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