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研究課題名（和文）複製活性を保持した精製複製複合体からＨＣＶ複製に関与する宿主因子の同定と解析

研究課題名（英文）Detection of host factors involved in active HCV replication complex

研究代表者
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研究成果の概要（和文）：C型肝炎ウイルス(HCV)の複製・翻訳の調節メカニズムについては不明である。そこで、複製だけでなく、粒子形成においても必須なNS5Aに注目し、NS5A結合膜タンパク質の複製・翻訳における役割を解析した。NS5A発現細胞からpull-down法によりNS5A結合膜タンパク質を精製し，プロテオーム解析、siRNA screeningにより翻訳および複製に関与しているタンパク質としてembryonic lethal, abnormal vision, drosophila-like 1 (ELAVL1)を見出した。ELAVL1はHCV RNAの翻訳・複製を調節する宿主因子である可能性が示唆された。

研究成果の概要（英文）：Although several host cellular proteins have been identified as NS5A-binding partners and their significance in the viral replication has been reported, the molecular basis of NS5A in Hepatitis C virus (HCV) life cycle has not been fully understood yet. In this study, to identify novel cellular factors interacting with NS5A, we performed a co-purification, pull-down approach using the cytoplasmic membrane fraction of cells expressing an epitope-tagged NS5A. We identified embryonic lethal, abnormal vision, drosophila-like 1 (ELAVL1) for both viral RNA replication and protein translation. We are going to elucidate the molecular mechanisms that modulate HCV life cycle through interaction between NS5A and host factors identified in our screening system.

研究分野：　Virology

キーワード：　C型肝炎ウイルス　翻訳・複製調節

１．研究開始当初の背景

ウイルスの複製はウイルス RNA 合成と蛋白翻訳の 2 つのステップに分けられる。共通の RNA をテンプレートにしていることから、効率よくウイルスが複製するためには、RNA 合成と翻訳は互いに協調する必要性があるものと考えられる。しかしながら、それらの調整機構はわかっていない。

２．研究の目的

C 型肝炎ウイルス(HCV)をモデルに RNA 合成と翻訳の調節メカニズムを明らかにすることで、多くの生物における RNA 合成と翻訳の協調性を明らかにすることが期待できる。

３．研究の方法

ウイルス複製複合体を内包する膜小胞内での HCV RNA 複製に関与するだけでなく、粒子形成においても重要な NS5A に注目し、NS5A 結合膜蛋白の翻訳・複製における調節機構を解析した。

４．研究の成果

NS5A 発現細胞から pull-down 法により NS5A に結合する膜蛋白を精製し，プロテオーム解析等を行い、翻訳および複製過程に関与している蛋白として embryonic lethal, abnormal vision, drosophila-like 1 (ELAVL1) を見出した。ELAVL1 の細胞内発現を調べたところ、レプリコン細胞では HCV 複製複合体が存在すると考えられている界面活性剤不溶性分画(DRM)に移行していた。HCV 翻訳・複製が低下した ELAVL1 ノックダウンレプリコン細胞に各種 ELAVL1 の欠損変異体を発現させた実験から、ELAVL1 が HCV RNA と結合し、さらに NS3、NS5A 蛋白と結合することで複製の場 DRM へ移行するものと考えられた。また、膜分画のトリプシン処理、ヌクレアーゼ処理により、主に複製は二重膜小胞(DMV)内側、翻訳は DMV の外側で行われているものと考えられた。

以上の結果から、ELAVL1 はゲノム複製により新規合成された HCV RNA と結合して、ウイルスタンパク質翻訳を誘導した。さらに、ELAVL1 は産生された NS タンパク質と結合して、HCV RNA を複製複合体へリクルートするものと考えられた。ELAVL1 は HCV RNA の翻訳・複製を調節する宿主因子である可能性が示唆された。

５．主な発表論文等

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〔産業財産権〕

○出願状況（計０件）

○取得状況（計０件）

〔その他〕

ホームページ等

http://www.nih.go.jp/niid/ja/from-vir2.html

６．研究組織

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