



Title	Analysis of the Functional Role of TIMM29 in the Hepatitis B Virus Life Cycle
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論文内容の要旨

Synopsis of Thesis

氏 名 Name	LIMIA MOHAMED ELDIRDIRI ABUELDAHAB
論文題名 Title	Analysis of the Functional Role of TIMM29 in the Hepatitis B Virus Life Cycle (B型肝炎ウイルス生活環におけるTIMM29の機能的役割に関する解析)
論文内容の要旨 〔目的(Objective)〕 Hepatitis B virus (HBV), the causative agent of chronic hepatitis B, remains a major global health concern, affecting an estimated 296 million people worldwide and leading to liver cirrhosis and hepatocellular carcinoma. HBV closely interacts with host organelles and proteins to facilitate its replication and persistence. Understanding these virus–host interactions is critical for identifying novel therapeutic targets. Our previous study identified the mitochondrial protein TIMM29 as a negative regulator of HBV transcription through its interaction with the viral preS1 domain, part of the large envelope protein. However, the precise molecular mechanisms by which the preS1–TIMM29 interaction mediates transcriptional repression remain unclear. In this study, we sought to elucidate these mechanisms to better understand how HBV exploits mitochondrial pathways for transcriptional control. Targeting such host-mediated suppression pathways could provide a promising strategy for developing future HBV treatments with a reduced risk of antiviral resistance. 〔方法ならびに成績(Methods/Results)〕 Here, we established Halo-TIMM29wt (full-length), Halo-TIMM29: Δ99–192 (deleted preS1-binding domain), or Halo-TIMM29: 92–194 (maintains preS1 binding but not mitochondria localization domains) expressing cells using TIMM29-knockout HB611 (TIMM29KO/HB611; HB611KO) cells, a Huh6-derived line stably producing HBV using HBV. HBV antigen expression and replication were markedly reduced in cells expressing TIMM29wt but not in those expressing deletion mutants. This indicates that TIMM29’s anti-HBV function depends on the 99–189 amino acid region that interacts with preS1. The Halo-TIMM29: 92–194 mutant, which failed to restore antiviral activity despite containing the preS1-binding region, suggested that mitochondrial localization is essential for TIMM29-mediated HBV suppression. In TIMM29-knockout C4 cells (TIMM29KO/C4; C4KO), an NTCP-expressing HepG2 line supporting HBV infection, all constructs exhibited a potent downregulation of HBeAg and HBsAg expression, intracellular core-associated and extracellular particle-associated HBV DNA, without affecting cccDNA formation, indicating that TIMM29 affects post-attachment/entry events of HBV. Gene expression microarray analysis revealed reduced levels of ARRDC3 and BASP1 in both TIMM29KO/HB611 and TIMM29KO/C4 cells, suggesting that mitochondrial TIMM29 functions as a signaling hub that promotes ARRDC3 and BASP1 expression to restrict HBV transcription. ARRDC3 expression depended on the preS1-binding region (aa 99–189) of TIMM29 in both cell types, whereas BASP1 regulation varied—being reduced in HB611KO cells but increased in C4KO cells—indicating cell-type-specific control mechanisms. Forced expression of ARRDC3 and BASP1 levels suppressed HBV gene expression and replication in both HB611 and C4 cells, supporting their antiviral roles. Expression of HBV large surface protein (LS) facilitated the degradation of TIMM29, ARRDC3, and BASP1 via the ubiquitin–proteasome pathway, while the middle surface protein (MS) had no effect. During HBV infection, their levels decreased in parallel with increased LS expression. 〔総括(Conclusion)〕 In conclusion, TIMM29 suppresses HBV transcription and replication by activating ARRDC3 and BASP1. While ARRDC3 regulation is largely dependent on the TIMM29–preS1 interaction, BASP1 appears to be influenced by additional, cell-type-specific factors. These findings uncover a novel TIMM29-centered antiviral axis that controls HBV replication and suggest potential targets for the development of innovative antiviral strategies.	

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

本研究は、B型肝炎ウイルス（HBV）の複製を制御する新たな宿主因子として、ヒトミトコンドリア膜タンパク質TIMM29の役割を明らかにしたものである。TIMM29がHBV表面タンパク質preS1と直接結合することに注目し、その抗ウイルス機構を分子レベルで精査した。構造改変を加えたTIMM29変異体を用いた機能解析の結果、HBV複製の抑制には、preS1結合ドメインとミトコンドリア局在の両方が不可欠であり、さらにその作用は細胞種に依存して異なることが示された。加えて、TIMM29はARRDC3およびBASP1といった宿主遺伝子の発現を誘導し、これらがHBV複製の抑制に寄与することも確認された。これらの知見は、ウイルス複製に対する宿主因子の新たな関与を示すものであり、HBVの病態理解や今後の治療標的の探索に対して意義深い情報を提供している。以上を踏まえ、本論文は博士（医学）の学位授与に値すると考える。