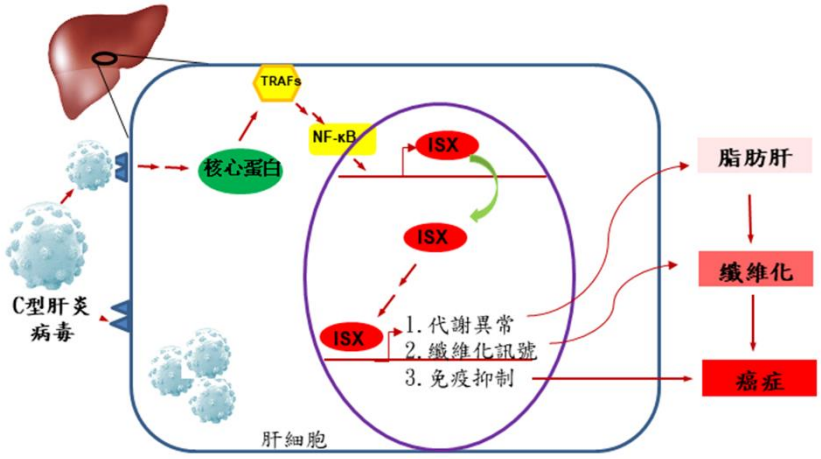
許世賢 教授 醫學院/醫學研究所

慢性 C 型肝炎病毒（HCV）感染是全球公共健康的一大挑戰。然而，對於病毒如何改變新陳代謝和免疫反應的機制，仍知之甚少。轉錄組學研究和多項證據表明，HCV 核心蛋白與腸道特異性箱形基因（ISX）的相互作用促進了一系列代謝、纖維化及免疫調節因子（如犬尿氨酸、PD-L1 和 B7-2）的表達，這些因子在體內外均能調節與 HCV 感染相關的致病性。在基因轉殖小鼠模型中，HCV 核心蛋白-ISX 軸能加劇代謝紊亂（特別是脂質和葡萄糖代謝）及免疫抑制，最終在高脂飲食（HFD）誘導的疾病模型中，促進慢性肝纖維化的發展。機制上，帶有 HCV JFH-1 複製子的細胞會促進 ISX 的表達，這是藉由核心蛋白誘導的 NF-κB 信號傳導實現的，進而導致代謝、纖維化及免疫調節因子表達的增加。相反，使用特異性 ISX shRNA 的細胞能有效抑制 HCV 核心蛋白引發的代謝紊亂和免疫抑制。在臨床上，HCV 感染的肝癌患者(HCC)中，HCV 核心蛋白的表現與 ISX、IDO、PD-L1 和 B7-2 的表現均顯著正相關。因此，該研究強調了 HCV 核心蛋白-ISX 軸在 HCV 誘導慢性肝病發展中的重要作用，並可能成為臨床上有潛力的治療靶點。



C型肝炎病毒調控腸道特異性箱型基因（ISX）促進慢性肝炎、纖維化、代謝異常及免疫抑制之發生。 在機制上，C型肝炎病毒感染藉由其核心蛋白誘導NF-κB 信號促進 ISX的表現，進而促使代謝、纖維化訊號和免疫抑制基因（KYN、PD-L1 和 B7-2）的表現。 TRAFs: 腫瘤壞死因子受體相關因子

【具體成果】

1. 113 年補助大專校院研究獎勵

2. 113 年特殊特殊優秀教研人才彈性薪資

【研究團隊】

團隊成員：

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團隊簡介：團隊研究方向為探討新穎的致癌基因在癌症上的機制探討。此外還研究了免疫細胞如何促進免疫反應的調節並影響各種疾病的進展，加深我們對腫瘤免疫相互作用的理解，並確定潛在的治療靶點，以改善治療策略。

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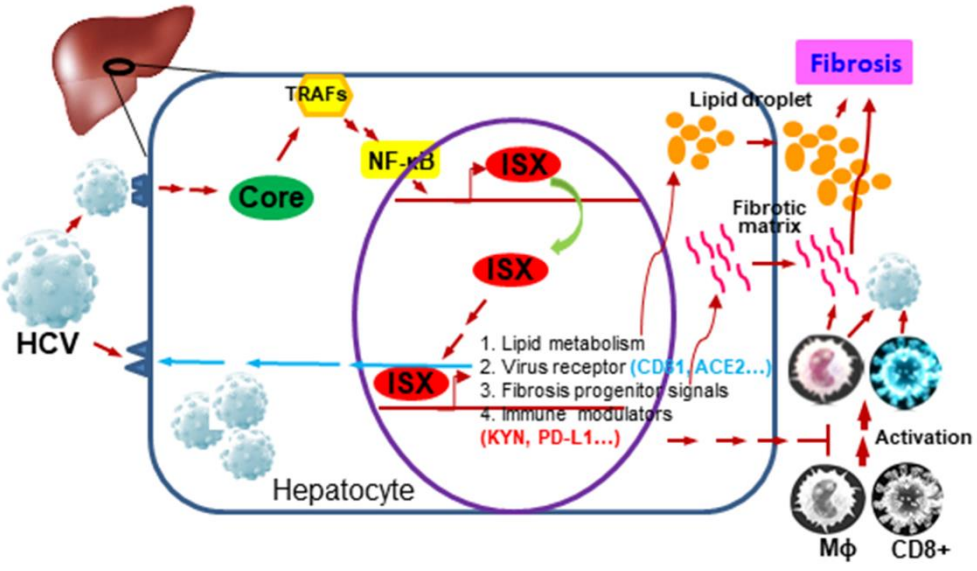
Chronic hepatitis C virus (HCV) infection poses a significant global public health challenge. However, the mechanisms by which the virus alters metabolism and immune responses remain poorly understood. Transcriptomic studies and various lines of evidence indicate that the interaction between the HCV core protein and the intestinal-specific box gene (ISX) promotes the expression of metabolic, fibrotic, and immunoregulatory factors, such as kynurenine, PD-L1, and B7-2. These factors regulate the pathogenicity associated with HCV infection both in vivo and in vitro.

In transgenic mouse models, the HCV core protein-ISX axis exacerbates metabolic disorders, particularly affecting lipid and glucose metabolism, as well as immunosuppression, ultimately driving chronic liver fibrosis in high-fat diet (HFD)-induced disease models. Mechanistically, cells harboring the HCV JFH-1 replicon upregulate ISX expression through core protein-induced NF-κB signaling, leading to increased levels of metabolic, fibrotic, and immunoregulatory factors. Conversely, treatment with specific ISX shRNA effectively inhibits the metabolic disorders and immunosuppression triggered by the HCV core protein.

Clinically, in HCV-infected liver cancer (HCC) patients, the expression of the HCV core protein is significantly positively correlated with the expression of ISX, IDO, PD-L1, and B7-2. This study highlights the critical role of the HCV core protein-ISX axis in the progression of HCV-induced chronic liver disease and suggests it as a potential therapeutic target in clinical settings.



【Concrete Results】

1. 2024 Special Outstanding Talents of the Ministry of Science and Technology Awards, Ministry of Science and Technology (MOST), R.O.C., Taiwan.
2. 2024, Merit Pay Implementation Program for Recruiting and Retaining Special, Outstanding, and Talented Faculty Members for Taiwanese Universities, Ministry of Education (MOE), Taiwan, ROC.

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