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An HCV E2-derived immunoadhesin independently targets to human hepatocytes and is internalized in a rate-limited manner determined by receptor density

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The envelope of the hepatitis C virus (HCV) mediates entry into cells by binding to receptors CD81, scavenger receptor BI and claudin-1 and then by fusing viral and cellular membranes following endocytosis, acidification of endosomes and binding to the Niemann-Pick C1-like cholesterol absorption receptor (NCP-1). All known HCV-receptor interactions are mediated by HCV envelope protein 2 (E2), but the manner in which E2 coordinates interactions with multiple entry receptors and cell surface cofactors to promote viral entry are only beginning to be understood. Here, we have developed soluble recombinant forms of E2 protein fused to the Fc-region of human IgG for use in the dissection of E2 function and as molecular probes to interrogate the early events of the E2-dependent HCV entry pathway. These recombinant E2-immunoadhesins retain the immunological profile and the cell surface and CD81-binding specificity typical of native E2. We now demonstrate that E2, in the complete absence of all other viral protein, is competent for both targeted binding and internalization into hepatoma cells. The rate of E2-Fc internalization differs between cell types and is, in part, dependent on the density of CD81 receptors displayed on the cell surface. Internalized E2-immunoadhesin localizes with markers of endocytosis and accumulates in late endosomes in target cells. Though binding to CD81 promotes and enhances the rate of E2 internalization, high level expression and display of CD81 is not sufficient to drive internalization of E2 in cells; confirming that recruitment of CD81 to a multi-component entry complex is a critical event in the rapid attachment and endocytosis of E2.

Biography

Ahmad Alshehri has completed his Bachelor's degree in Medical Laboratory Sciences from King Khalid University, Saudi Arabia and Master of Science in Biomedical Sciences from University of Hull at England. He is also a recipient of a Prize Studentship from The Cultural Bureau of the Royal Embassy of Saudi Arabia to continue his PhD degree at Medical Research Institute of Dundee University, Scotland.

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