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Dysregulation and interaction of metabolic pathways for glucose homeostasis, insulin signaling and autophagy in Hepatitis C Virus-induced insulin resistance and implication in therapeutic development

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Hepatitis C virus (HCV) infection is a global health problem affecting over 200 million individuals. Currently, there is no vaccine or effective therapy. It is considered as a metabolic disease; chronic infection induces insulin resistance (IR), which is the pathogenic foundation for metabolic syndrome, type 2 diabetes mellitus (T2DM) and liver diseases including hepatocellular carcinoma. Development of IR not only accelerates the progression of liver disease, but also makes IFN-based therapy less-responsive. Understanding of the molecular basis of IR and response to conventional therapy is pivotal for the development of a novel one. Insulin receptor substrates (IRS-1 and IRS-2) are the mediators for insulin signaling pathways through downstream PI-3K/Akt. IRS-1 is phosphorylated at Ser312 and IRS-2 is virtually undetected in infected cells. Our central hypothesis is: Both IRS1 and IRS2 are involved in HCV-IR, the former through IRS-1 Ser312 phosphorylation and the latter through down regulation by microRNAs. The metabolic pathways for glucose homeostasis, insulin signaling and autophagy are dysregulated in infected cells. Defects in glucose homeostasis results from the inactivation of glycogen synthase (GS) by Ser641 phosphorylation and of inactivating phosphorylation of GSK-3 β Ser641. Insulin signaling was impaired by IRS-1 Ser 312 phosphorylation followed by dysregulation of Akt pathway. Active autophagy is revealed by the formation of LC3 puncta and upregulation of Beclin 1 and Atg5-Atg12 conjugate. These pathways interact as IRS-1 Ser312, Beclin 1 and its negative regulator (Bcl-XL) are present together in an immunocomplex. Inhibition of autophagy by 3-MA also reduces phosphorylation of IRS-1 Ser 312 and Gs Ser 641. They are activated within 2 weeks p.i., but undergoes possible alteration of protein modification and expression. It appears that GSK-3 is the master communicator, controlling multiple feed-back loops. The inactivating phosphorylation of GSK-3 β and of GS Ser641 is inhibited in IFN-cured cells. The energy sensors mTOR and AMPK are activated in infected cells which are also inhibited by IFN α implicating potential as therapeutic targets. Our results suggest that unraveling the molecular basis of IR and developing strategies to regulate multiple IRS-1 mediated pathways simultaneously may lead to a better therapeutic outcome.

Biography

Gokul C Das is currently a member of the faculty in the Department of Medicine, of the Center for AIDS research, Center for Drug Discovery and of the Dan L Duncan Cancer Center at the Baylor College of Medicine (BCM), Houston. Previously, he was a professor of molecular biology at the University of Texas Health Science Center at Tyler (UTHSCT). Dr Das had his Ph.D. degree in Biophysics from the University of Kolkata, India. After his postdoctoral work at the Institute de Biologie Moléculaire et Cellulaire du CNRS, Strasbourg, France and at the Oak Ridge National Laboratory, Oak Ridge, TN, he was a visiting scientist at NIH working on DNA tumor viruses. He continued his interest as a Professor of Molecular Biology at UTHCT. His Current interest is to understand molecular pathways in pathogenesis induced by Hepatitis C Virus (HCV) and HIV, or in HCV-HIV co-infection, and to use both a cellular and humanized animal model to develop antiviral strategies. Dr Das is currently on the editorial board of a number of international journals. He was the recipient of international guest scientist awards (1997, 2000) from the Ministry of Science and Technology, Japan and was a member of the biotechnology delegation to China.

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