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Interaction of molecular pathways in Hepatitis C Virus induced insulin resistance and IFN-based therapy

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Abstract

Chronic hepatitis C virus (HCV) infection is considered as a metabolic disease; it induces insulin resistance (IR) as the pathogenic foundation for metabolic syndrome, type 2 diabetes milletus and liver diseases including hepatocellular carcinoma. Development of IR makes IFN-based therapy non-responsive. The molecular basis of IR and non-response to therapy is not well understood, but insulin receptor substrates (IRS-1 and IRS-2) mediated pathways are implicated. We hypothesize that both IRS's are involved, IRS-1 through phosphorylation at Ser312, and IRS-2 through down regulation by mi RNAs. In persistently infected liver cell model, the pathways for glucose homeostasis (IRS-1—Akt—GSK-3—GS) and insulin signaling (IRS-1-PI-3K/Akt) are dysregulated and it also elicits autophagy as a contributory factor to IR. Inactivating phosphorylation of GSK-3β Ser 9 and of GS Ser641 is inhibited in IFN-cured cells. These pathways are activated early and interact as Beclin 1, its negative regulator Bcl-XL and IRS-1 Ser 312 are present in the same immunocomplex. The energy sensors mTOR and AMPK are also activated by phosphorylation and inhibited by IFN α. We find that IRS-2 is a possible target for miRNAs especially for hsa-let -7i/7e. In cells cured by IFNα, these are down regulated and is accompanied by the up regulation of several other mi RNAs related to IR, PI-3K-Akt or apoptosis pathway. Our results suggest that pathways leading to IR are activated early in infection and IRS-1/2 mediated pathways, with regulatory feed- back loops connecting GSK-3, are involved in the development of IR and therapeutic response.

Biography:

Gokul C Das, Ph.D, is a member of the faculty in the Department of Medicine at Baylor College of Medicine and of the center for AIDS research, Center for Drug Discovery and Dan-L Duncan Cancer Center. He is an ex-Professor of the Department of Molecular Biology, University of Texas Health Science Center at Tyler. His long term interest is in biological carcinogenesis, both DNA and RNA viruses, and therapeutic development. He has published significantly in first rated journals, serves in the editorial boards and as reviewers of a number of journals of repute. He was a recipient of international guest scientist award from Japanese Government and a member of the biotechnology delegtion to China.