OMICS Group Conferences
Accelerating Scientific Discovery

2nd World Congress on
Virology

August 20-22, 2012 Embassy Suites Las Vegas, USA

Proteomic analysis indicates the association of calreticulin down-regulation and cyclophilin A up-regulation with Type I interferon antagonism of Japanese encephalitis virus NS5 protein

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Japanese encephalitis virus (JEV) non-structural protein 5 (NS5) exhibits a type I interferon (IFN) antagonistic function. This study intends to characterize the type I IFN antagonism mechanism of JEV NS5 protein using proteomic approaches. TE-671 human neuroblastoma cells transfected with the control vector and NS5-expressing plasmid were tested their responses to interferon (IFN)-β; the expression profiles of transfected cell lines were analyzed using two-dimensional electrophoresis (2-DE) and mass spectrometric (MS). JEV NS5 reduced IFNβ-induced responses, e.g. IFN-sensitive response element (ISRE) promoter activity, mRNA expression of PKR and OAS, phosphorylation of STAT1 and STAT3. Proteomic analysis and Western blotting demonstrated JEV NS5 up-regulating peroxiredoxin-1, heat shock protein 60, stress induced phosphoprotein 1, and cyclophilin A, and down-regulating heterogeneous nuclear ribonucleoprotein H3, prohibitin, thioredixin and calreticulin in human medulloblastoma TE671 cells in the presence of IFNβ. Calreticulin down-regulation and cyclophilin A up-regulation implied the activation of Ca2+-depedent phosphatase calcineurin. The calcineurin inhibitor, cyclosporin A (CsA), sensitized IFNβ-induced responses in NS5-expressing cells. Importantly, the combined treatment of CsA and IFNβ induced a time-dependent increase of STAT1, STAT3, mTOR and AKT phosphorylation in NS5-expressing cells. The combined treatment of CsA and IFNβ also activated mRNA expression of IFN-stimulated genes, showing more potently inhibitory effects on virus yield. JEV NS5 induced calreticulin down-regulation and cyclophilin A up-regulation, being associated with Type I interferon antagonism via the activation of Ca2+-depedent phosphatase calcineurin. This study shows insights into a possible mechanism of Type I interferon antagonism by JEV NS5, being applicable for elucidating JE pathogenesis.

Biography

Professor Cheng-Wen Lin has completed his Ph.D from National Tsing-Hua University in 2003. He is the Dean of Student Affairs in China Medical University since 2009. He has published more than 50 papers in reputed journals.

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