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Novel insights into the regulation of alternative NF-kB pathway: A promising step towards understanding obesity associated disorders

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Abstract

Obesity has been a growing health concern, which has been associated with several inflammatory and metabolic disorders as well as cancer. NF-kB signalling has been associated with various diseases such as inflammatory and metabolic disorders. Although significant insight has been gained in our understanding of the classical NF-kB pathway and its association with obesity-induced inflammation, the role of alternative NF-kB pathway in these processes has remained elusive. Recently, it has been shown that NF-kB inducing kinase (NIK) plays an essential role in obesity induced glucose intolerance and that the hepatic levels of NIK are elevated in obese mice. How obesity induces the levels of NIK and the mechanism by which NIK levels are regulated has remained unclear. Therefore it is essential to study the mechanism by which hepatocyte NIK levels are regulated. Importantly, it remains to be studied whether loss of control over cellular NIK levels would result in glucose intolerance. Recent findings indicated that TNF receptor associated factors (TRAF) TRAF3, TRAF2 and cIAP play an important role in negatively regulating the alternative pathway by controlling the turnover of NF-kB inducing kinase (NIK), an essential kinase in the alternative NF-kB pathway. In resting cells TRAF3 forms a bridge between NIK and TRAF2-cIAP2 complex via its TRAF domain. In this complex cIAP2 acts as a E3 ubiquitin ligase that mediates K-48 linked ubiquitination of NIK leading to the proteasome dependent degradation of the latter. Deletion of TRAF3 or TRAF2 or cIAP disrupts the NIK-TRAF3-TRAF2-cIAP complex that results in NIK stabilization and constitutive activation of the alternative pathway. Interestingly, as mentioned above, obese mice displayed higher levels of NIK in the liver. It is interesting to investigate whether obesity facilitates NIK to escape degradation by TRAF3-TRAF2-cIAP complex and whether loss of hepatocyte TRAF3 or TRAF2 or cIAP would result in glucose intolerance and/or enhance other inflammatory and metabolic disorders induced by obesity. Collectively, it appears that tight regulation of the alternative pathway is essential to prevent inflammatory and metabolic disorders induced by obesity and that targeting this pathway would be beneficial in the prevention of obesity induced disorders.

Biography

Sivakumar Vallabhapurapu (Siva) is a Assistant Professor in the Department of Cancer and Cell Biology, University of Cincinnati, Cincinnati, Ohio, USA. He completed his graduate training in 2004 at the University of Karlsruhe, Karlsruhe, Germany, and was a postdoctoral fellow at the Fritz Lipmann Institute for Age Research in Jena, Germany and at the University of California, San Diego. At UCSD he worked with Dr. Michael Karin (one of the world's leading scientists in the study of cellular signaling pathways) and worked on regulation of NF-kB signaling. Siva has published very high impact papers in journals such as Nature Immunology, Science, Journal of Experimental Medicine etc., and has also contributed significantly to the field of NF-kB signaling by writing a review on NF-kB signaling in the immune system, published in the journal Annual Reviews of Immunology.