Cell Communication and Signaling BioMed Central

Meeting abstract

Open Access

Proteomic identification of the tyrosine phosphatase SHP1 as a novel LMP1 interaction partner, which mediates autoregulation of LMP1 signaling

J Griese*[1], T Knoefel[1], H Kutz[1], SM Feller[2] and A Kieser[1]

Address: [1]Helmholtz Zentrum München, Dept. of Gene Vectors, Signal Transduction Group, München, Germany and [2]Cell Signalling Group, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK

* Corresponding author

from 12th Joint Meeting of the Signal Transduction Society (STS). Signal Transduction: Receptors, Mediators and Genes
Weimar, Germany. 29–31 October 2008

Published: 26 February 2009

Cell Communication and Signaling 2009, **7**(Suppl 1):A45 doi:10.1186/1478-811X-7-S1-A45

This abstract is available from: http://www.biosignaling.com/content/7/S1/A45

The Epstein-Barr virus (EBV) oncoprotein LMP1 (latent membrane protein 1) mimics a constitutively active receptor molecule. It contributes to viral cell transformation by the activation of NF-kappaB, JNK/AP1, MAPK, JAK/STAT and PI3-kinase signaling. LMP1 recruits TRAF1-3, 5 and 6, TRADD and RIP1, which are also known as signaling mediators of Toll-like and tumor necrosis factor-receptors. Here, we established a functional proteomics approach to identify novel interaction partners of the LMP1 signaling domain. This approach led to the characterization of the tyrosine phosphatase SHP1 as a direct binding partner of LMP1. Interaction of SHP1 with LMP1 was verified in primary human B-cells, which had been transformed with a recombinant EBV carrying a HA-tagged LMP1 allele. The SHP1 binding site of LMP1 is located within the membrane-proximal region of the LMP1 signaling domain and shows no overlap with known protein interaction domains of LMP1. The unique sequence of this site does not resemble known SHP1 interaction motifs of cellular proteins. Mutation of the SHP1 site caused the loss of SHP1 binding to LMP1 in EBV-transformed human B-cells. SHP1 has previously been described as a negative regulator of growth factor or immune receptor signaling by dephosphorylating e.g. tyrosine kinases such as JAKs or SRC kinases. LMP1 induction of the NF-kappaB pathway was greatly enhanced in SHP1-knockout DT40 B-cells as compared to wildtype cells. This effect was reverted by reconstitution of SHP1 expression in the SHP1-KO cells. Also mutation of the SHP1 interaction site or the co-expression of a dominant-negative SHP1 caused hyperactivation of NF-kappaB signaling and JAK3 hyperphosphorylation by LMP1. Because the SHP1 interaction site of LMP1 mediates inhibitory effects on LMP1 signaling, we named this region CTIR1 (C-terminal inhibitory region 1). In summary, the proteomic analysis of the LMP1 complex revealed a novel autoregulatory mechanism of oncogenic LMP1 signaling, which limits its own activity through the recruitment of a tyrosine phosphatase. This mechanism might be of high relevance for the survival of EBV-transformed cells because LMP1 hyperactivity is known to be toxic for the target cells.