Cell Communication and Signaling BioMed Central

Meeting abstract

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Pertussis toxin blocks growth factor receptor signalling by attenuating p21ras activity

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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):A44 doi:10.1186/1478-811X-7-S1-A44

This abstract is available from: http://www.biosignaling.com/content/7/S1/A44

Pertussis toxin (PTX), a *Bordetella Pertussis* exotoxin, has been recently shown to prevent growth factor-induced activation of the extracellular signal regulated protein kinases ERK1 and ERK2. Due to its capacity to ribosylate inhibitory GTP-binding proteins of the Gi/o family, the antiproliferative effect of PTX is generally thought to originate form interference with growth factor receptor-induced inhibitory signal transduction pathways. However, in human embryonic kidney (HEK293) cells, we could recently demonstrate that attenuation of inhibitory Gi/o signaling by the regulator protein Goloco failed to affect epidermal growth factor (EGF) receptor-induced ERK1/2 activation. In addition, Goloco also failed to interfere insulin-like growth factor (IGF-1) receptor associated ERK1/2 signaling, indicating that PTX must affect ERK1/2 signalling by mechanism other than inactivation of Gi/o function. The small GTP-binding protein p21ras plays a central role in mitogenic signalling, as it connects a number of growth factor receptors to the raf-1/MEK/ERK1/2 signalling module. Western blot experiments revealed that pre-treatment of HEK293 cells with PTX prevents translocation of p21ras to the plasma membranes. Moreover, immune-precipitation experiments also showed that PTX prevents interaction of p21ras with raf-1 kinase. A similar finding was observed after pre-treatment of the cells with mevastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. Mevastatin treatment resulted in a loss of p21ras from the plasma membrane, inhibited EGF-induced p21ras/raf-1 interaction and ERK1/2 activation. These results indicate that, besides of its inhibitory action on Gi/o signalling pathways, PTX may also interfere with growth factor-mediated ERK1/2 activation by attenuating p21ras activation.