Cell Communication and Signaling BioMed Central

Meeting abstract

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Tfg (Trk fused gene) is a Carma-1/IKKγ interacting protein involved in CD40-induced canonical NF-κB signaling

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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):A4 doi:10.1186/1478-811X-7-S1-A4

This abstract is available from: http://www.biosignaling.com/content/7/S1/A4

Carma-1 is required for B cell receptor-/CD40- and T cell receptor-/CD28-induced B- and T-cell activation via JNK and NF-βB. In B cells, Carma-1 becomes phosphorylated by PKCβ, leading to its oligomerization. Subsequent Bcl10 binding induces IKKβ-activation and, thereby, canonical NF-κB signalling. Despite these findings it is still unknown how exactly Carma-1 is connected to the plasma membrane and to the IKK-complex. Therefore, we purified Carma-1 complexes from mouse CH12 B cells using anti-Carma-1 affinity columns. Mass spectrometric analyses of the column eluates demonstrated the presence of Carma-1 as well as three previously uncharacterized adaptor proteins in B cells, one of which was the Trk-fused gene (Tfg), an adaptor protein containing PB1 and coiled-coil domains. Whereas Tfg was originally identified as fusion partner of oncogenic Trk tyrosine kinase mutants, the normal cellular homologue of Tfg has so far not been described in B cells. However, Tfg has been shown in other systems to interact with IKKγ and to enhance TNF-induced NF-κB activation.

Tfg and Carma-1 co-localized at the plasma membrane and perinuclear structures in B cells. We further corroborated the interactions of Tfg, IKKγ and Carma-1 by Blue Native gel electrophoresis, where Carma-1 and Tfg formed a 0.7–1 MDa complex. Ectopic expression of Tfg increased the molecular mass of IKKγ complexes, fused IKKγ, Bcl10 and Carma-1 complexes to a ~2 MDa complex, and increased basal and CD40-induced canonical activity of NF-κB and IKKβ. In contrast, shRNA-mediated silencing of Tfg decreased CD40-induced IKKβ activity.

Very interestingly, in primary B cells, highest expression of Tfg was detected in marginal zone and B1 B cells, and Carma-1 and Tfg formed complexes in these B cells. Since Carma-1 is required for marginal zone B cell and B1 B cell development, we suggest that a functional interaction between Carma-1 and Tfg contributes to development and maintenance of these cells by means of canonical NF-κB signals.