Protein Tyrosine Phosphatase Pez:

Its role in the regulation of cell-cell adhesions

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Abstract

The balance of tyrosine phosphorylation in the cell is maintained by the opposing actions of protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs). Investigation into tyrosine phosphorylation was initially focused on the action of PTKs. However, research over the past decade has revealed that PTPs also play a key role in signal transduction.

The multi-protein complexes that constitute the cell-cell adhesions in endothelial and epithelial tissues are dynamically restructured in response to extracellular and intracellular signalling. Tyrosine phosphorylation is involved in the regulation of both adherens junctions and tight junctions. Inhibitors of PTPs have been shown to disrupt cell-cell adhesions indicating that PTPs are important in maintaining adhesion integrity.

The maintenance of a selectively permeable barrier is an essential function of endothelial cells, which are the cells that line the lumen of blood vessels. Therefore, it is important to understand the normal functioning of the proteins in the cell-cell adhesion complexes. The aims of this research were to ascertain which members of the PTP family are expressed in human umbilical vein endothelial cells (HUVEC) and to characterise a PTP that may potentially be involved in the regulation of cell-cell adhesions.

A homology screen identified a cytosolic phosphatase, PTP-Pez, to be highly expressed in HUVEC. The presence of the protein-protein interaction FERM domain (band 4.1, ezrin, radixin and moesin) at the N-terminus of Pez predicted its localisation to the plasma membrane. Specific antibodies showed that in confluent monolayers Pez is cytoplasmic and concentrated at intercellular junctions but the protein is nuclear in sub-confluent cells. The adherens junction protein β-catenin and the tight junction protein occludin were both identified as potential substrates of Pez using a "substrate-trapping" approach. Data showing that Pez bound to and dephosphorylated β-catenin *in vivo* further substantiated this. A truncated form of Pez lacking the catalytic domain acted as a dominant negative mutant inhibiting the dephosphorylation of its

substrates at intercellular junctions and enhancing cell motility. Canine epithelial cells overexpressing Pez underwent an apparent epithelial to mesenchymal transition (EMT), a process typified by downregulation of cell-cell contacts. These findings indicate that Pez plays a role in the regulation of cell-cell adhesion.

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