

## **INTERACTION OF SPECTRIN WITH THE LOW MOLECULAR WEIGHT PHOSPHOTYROSINE PHOSPHATASE (LMW-PTP)**

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Spectrins are major components of the membrane skeleton. This protein scaffold is implicated in membrane stabilization, cell spreading, establishment of cell polarity and location of specific membrane proteins. Understanding the diversity of these functions requires to better characterize the complex interactions of these molecules with other cellular proteins through the study of specific modular interacting domains. Spectrin alpha II subunit contains an SH3 domain, the ligands of which have not been clearly identified yet.

By yeast two-hybrid screening of rat kidney and human lymphocyte cDNA libraries, we have found that spectrin SH3 domain binds isoform A of the LMW-PTP. Spectrin SH3 domain does not interact with isoforms B and C, although they are present in both tested libraries. LMW-PTP A does not interact with either the SH3 domain of spectrin alpha I subunit or other SH3 domains. Besides, mutations in spectrin SH3 domain abolish the interaction. Although LMW-PTP A is mainly a cytosolic enzyme, we have shown by western blot on a rat kidney cell line (RCCD1) that it is also present in the triton insoluble fraction along with the spectrin based-membrane skeleton.

The spectrin SH3 domain-LMW-PTP A interaction may have several functions: (i) Recruitment of this enzyme to its membrane substrates such as PDGF, EGF and insulin receptors. (ii) Dephosphorylation of spectrin itself since tyrosine phosphorylation can occur on spectrin. Using mutagenesis, we have identified one phosphotyrosine residue (Tyr 1176) which is located in the calpain cleavage site, near the SH3 domain. We have shown that this tyrosine is a substrate for the LMW-PTP A and that its phosphorylation can modify the sensitivity of spectrin to calpain. Thus, this suggests that Tyr 1176-phosphorylation state could modulate spectrin cleavage by calpain during membrane skeleton remodeling.