**Interaction of lysophosphatidic acid with signaling protein domains: affinity, stoichiometry and the site of binding.**

We demonstrated the selective and high affinity binding of the SH2 domain of Nck1 to LPA surfaces. ITC experiments suggest the existence of two sites (KD1=480 nM, n1=50, KD2=2000 nM, n2=150). The high-affinity site represents the binding of the domain to LPA surface, whereas the low-affinity site likely describes a structural rearrangement of the complex. We observed the domain binding to liposomes mimicking the inner leaflet of the plasma membrane with LPA or PIP-5-P, PIP-3,5-P2, and PIP-4,5-P2 lipids. Infrared spectrum of the domain corresponds to the published -helical and -sheet elements. Binding to LPA micelles affects its Tyr sidechains, while in the liposome systems its -helical elements. We validated the specific binding of SH2 domain to its known phosphopeptide. In the presence of monomeric LPA the affinity of the phosphopeptide to the domain is weakened, while LPA micelles disrupted the binding. This observation supports a competitive binding of the SH2 domain to either its target phosphopeptide or to the LPA surface.