Effects of Valence Switching on GRB2 and SOS-1 mediated Oligomerization of LAT: Theory and Simulation

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Recent experimental advances indicate that the aggregation of receptor, adaptor and effector proteins, to form multi-protein complexes, plays an important role in the initiation and propagation of intracellular signals. Formation of signaling complexes containing oligomers of the trans-membrane adaptor protein LAT has recently been identified as a critical step in TCR-mediated signaling. Cross-linking of LAT arises from the formation of a 2:1 complex between GRB2 and SOS1, which bridges two LAT molecules through the interaction of an SH2 domain on each GRB2 with a phosphotyrosine of each LAT. We have developed a mathematical model to describe this oligomerization and used it to determine both the steady-state distribution of LAT oligomers and the kinetics of oligomer formation. We find that the valence of LAT for binding GRB2, i.e., the number of LAT phosphotyrosines that can bind the GRB2 SH2 domain, is a critical factor in determining both the nature and extent of aggregation. The valence ranges from 0 to 3, but a dramatic rise in oligomerization occurs between valence 2 and 3, a phenomenon we call valence switching because the valence is controlled by the extent of phosphorylation of specific LAT tyrosines. Predictions from our model are in excellent agreement with the results from a rule-based stochastic simulation approach. In the event of valence switching, a sol-gel transition of the aggregating LAT is possible, as is indicated by both the theoretical and simulation approaches.