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Structural basis of membrane targeting of the toll-interacting protein

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The innate immunity-signaling network detects conserved molecular structures of pathogens through the action of Toll-like receptors (TLRs). The TLR signaling pathway is regulated by cytosolic intrinsic modulators such as the Toll-interacting protein (Tollip). Tollip is an adaptor protein with an N-terminal Tom1-binding domain, a central C2 domain, and a C-terminal CUE domain. Phosphoinositides and ubiquitin have been recently identified as physiological ligands for Tollip. We have demonstrated that the Tollip C2 domain preferentially interacts with phosphoinositides in a calcium-independent manner and that this association is critical for membrane targeting of the protein. Using a combination of functional and structural approaches, we have identified key phosphoinositide-binding residues located in a flexible region nearby the beta-groove of the protein. The CUE domain mediates Tollip dimerization and binds ubiquitin, although the structural basis of the interaction is unknown. We have identified the interface residues involved in Tollip CUE domain-ubiquitin association, suggesting that the Tollip CUE domain dissociates into monomers when bound to ubiquitin and that the Tollip CUE-ubiquitin complex reversibly associates with moderate affinity. Remarkably, we demonstrate that ubiquitin negatively regulates Tollip's phosphoinositide binding and this novel function is associated to direct binding to the Tollip C2 domain. This leads us to hypothesize that the association of ubiquitin to the Tollip's C2 and CUE domains negatively modulates Tollip's membrane targeting. Overall, our findings provide the basis to understand how Tollip is intracellularly partitioned in a ligand-dependent manner and how these molecular interactions modulate TLR signaling and membrane trafficking.

Biography

Daniel Capelluto has completed his Ph.D. in Biochemistry at the University of Buenos Aires and his postdoctoral structural biology studies at the University of Colorado Health Sciences Center. He is currently an Associate Professor in the Department of Biological Sciences at Virginia Tech. He has published ~25 papers in journals such as Nature, Cell, Journal of Biological Chemistry, and Journal of Immunology. The central theme of his research is to understand how membrane protein-lipid interactions drive intracellular signaling and modulate cellular processes ranging from the regulation of the innate immune response, endosomal membrane trafficking to blood coagulation.

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