

P014 How ArfGEFs couple stimulation of GDP/GTP exchange to membrane recruitment of Arf proteins

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Arf proteins are activated by GEFs with a conserved Sec7 domain. Intermediates of the GDP/GTP exchange reaction, from which GDP has not dissociated, can be trapped by BFA or a mutation of the invariant catalytic glutamate of the Sec7 domain. Their high resolution crystal structures (1) allow to reconstitute a «movie» of the exchange reaction. They show that Arf-GDP docks to the Sec7 domain in a conformation that cannot bind tightly to membranes. Conversion to the membrane-bound conformation occurs while GDP is still bound, and is necessary to bring the invariant glutamate of the Sec7 domain in a catalytic position. Thus, Sec7 domains have a dual function of securing Arf to membranes and stimulating GDP dissociation, and GEF-stimulated dissociation of GDP is structurally dependent on the prior recruitment of Arf to a membrane (which thus acts as a «co-factor» of the GEF). While the structure of full-length Arf-GDP-Sec7-BFA shows that BFA can bind to cytosolic Arf/Sec7 complexes, the crystal structure using an N-terminally truncated Arf mutant suggests that the drug may also trap the weakly membrane-bound Arf-GDP-Sec7 fraction to membranes. This may explain the reported effect of BFA in displacing Arf and ArfGEFs to membranes. (1) Renault L, Guibert B, Cherfils J. (2003) *Nature* 246, 525