In search for a role of oligomerization of a purine transporter in a model fungal system

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Running title: Role of oligomerization of a purine transporter

The uric acid/xanthine transporter UapA of the model fungus *Aspergillus nidulans* has been used as a prototype cargo to study membrane trafficking and endocytosis. In the presence of ammonium ions or substrates UapA is ubiquitinated, internalized from the PM and sorted into the MVB/vacuolar pathway. Interestingly, substrate-elicited endocytosis operates only for functional UapA molecules or for inactive UapA versions co-expressed with active UapA molecules. The latter phenomenon, called in *trans*-endocytosis, prompted us to investigate whether UapA oligomerizes. Here, we confirm that UapA oligomerizes using two different approaches; reconstitution of split YFP parts attached to UapA (BiFC assay) and by direct co-immunoprecipitation. Subsequently, using results from a systematic analysis of the N-tail of UapA, we select specific mutants showing ER-retention and show that UapA oligomerization takes place in the ER membrane. Thus, UapA oligomerization might serve either for ER-exit and trafficking to the plasma membrane, without excluding a role in the function and turnover of UapA *per se*. To approach these issues, we genetically selected suppressors of an ER-retained mutant, which are located in transmembrane segments (TMS) 7 and 11-12. Our findings are better explained with the hypothesis that the N-tail of UapA allosterically affects the structure of UapA so that it also affects its oligomerization, which in turn might affect trafficking and/or turnover. At present we examine the possible role of the Sec13/Sec23-24 ER-exit molecular machinery on UapA oligomerization and *vice versa*. Oligomerization has been observed in a number of plant and mammalian transporters, including those involved in neurotransmission, showing that it constitutes an evolutionary conserved mechanism for the fine regulation of transporters.