

P014 MLN64 and MENTHO, two mediators of endosomal cholesterol transport

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Metastatic Lymph Node 64 (MLN64) was identified as a gene overexpressed in malignant compared with benign breast tumours and is overexpressed in about 25% of breast cancers. MLN64 is composed of two conserved regions. The amino terminal contains a conserved membrane spanning MENTAL domain shared with a unique protein called MENTHO, and targets the protein to late endosome. The carboxy-terminal domain is composed of a cholesterol binding steroidogenic acute regulatory (StAR) protein related lipid transfer (START) domain exposed to the cytoplasm. MLN64 or MENTHO overexpression leads to the accumulation of enlarged endosomes an effect likely mediated by the MENTAL domain, suggesting that both proteins are involved in the endocytic compartment dynamics. Using photocholesterol binding assay, we find that the MENTAL and START domains of MLN64 are cholesterol-binding domains. Moreover, the MENTAL domain mediates homo and hetero-interaction of MLN64 and MENTHO. These data indicate that within late endosomes membranes, MLN64 and MENTHO define discrete cholesterol-containing subdomains. The MENTAL domain might serve to maintain cholesterol at the membrane of late endosomes prior to its shuttle through the START domain to cytoplasmic acceptor(s).