Annexin A2 in endosome biogenesis

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During endocytic membrane transport, cell surface molecules destined for late endosomes and lysosomes, e.g. epidermal growth factor (EGF) receptor and other downregulated signaling receptors, are sequentially incorporated into membrane invaginations with opposite topology. After internalization via clathrin-coated vesicles (or caveolae), which bud into the cytoplasm, and delivery to early endosomes, ubiqitinated receptors are sorted into intralumenal vesicles that form within multivesicular regions of the early endosome. These regions then detach — or mature — from early endosomes, giving rise to a multivesicular endosome (or multivesicular body, MVB). Eventually, lumenal vesicles and their protein cargo are delivered to late endosomes and lysosomes for degradation. The biogenesis of multvesicular endosomes thus involves the concomitant deformation of early endosomal membranes towards the cytosol (to form the endosome itself) and towards the endosome lumen (to form intralumenal vesicles). We find that the formation of intralumenal vesicles is controlled by the PI3P-binding protein SNX3, while EGF receptor sorting depends, as expected, on Hrs — another PI3P-binding protein. By contrast, our data suggest that the biogenesis of the endosome itself — but not the intralumenal invagination process — is regulated by actin patches, presumably because these patches drive the membrane remodeling process. We find that this mechanism depends on AnxA2, an actin binding protein, the actin nucleation factor Spire1, and Arp2/3, which is necessary for filaments branching. Similarly, we find that AnxA2 itself is also required, much like actin, for endosome biogenesis — but not for intralumenal invagination. This activity of AnxA2 in endosome biogenesis is regulated by phosphorylation of AnxA2 Tyr23, and does not seem to depend on the AnxA2 light chain p11/S100A10. Our data indicate that, during multivesicular endosome formation, SNX3 and AnxA2/actin regulate the deformation of early endosome membranes towards the cytosol and the lumen, respectively.