AMSH characterization and interaction with ESCRT-III CHMP3

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Inclusion of receptors into multivesicular bodies (MVBs) of the Endosomal Sorting Pathway (ESP) commits receptors to degradation via the lysosome. The protein machinery associated with MVB biogenesis is responsible both for the sorting of ubiquitinated receptor cargo to be incorporated into these vesicles, and the physical deformation of the membrane away from the cytosol. It is in this way that MVB formation can be considered morphologically similar to that of viral particle budding, and interest in the protein machinery responsible for MVB formation has greatly increased since the discovery that these proteins are necessary for budding of enveloped retroviruses such as HIV [1].

The numerous MVB proteins are broadly classified into four ESCRT complexes (Endosomal Sorting Complex Required for Transport), ESCRT-0, -I, -II and –III. However, whilst many of the ESCRT proteins and auxiliary proteins have been identified, their cooperative mode of action is still poorly understood. AMSH (Associated Molecule with the SH3 domain of STAM) was first identified as a binding partner of the STAM protein of ESCRT-0 [2], but has since been shown to bind clathrin [3] and a range of the CHMP (CHarged Multivesicular body Protein) proteins of the ESCRT-III complex [4], thus through AMSH exists a link between the initiating and the terminating ESCRT complexes. AMSH is a ubiquitin isopeptidase [3], which has led to the proposition of two potential roles within the ESP; rescuing ubiquitinated receptors, or removing the ubiquitin signal from the receptor cargo just before incorporation into vesicles. Through structural studies by x-ray crystallographic techniques of AMSH in complex with binding partners of the ESP this work aims to elucidate the action of AMSH, and more specifically how this is linked to recruitment of ESCRT-III proteins and the deubiquitinating activity of AMSH.

References

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