Epsins’ novel role in cancer cell invasion

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The epsin family of endocytic adaptors has been found to be upregulated in cancer; however the relevance of these findings to this pathological condition is unclear. We have recently demonstrated that epsins are required for cell migration. In fact, epsin overexpression promotes cancer cell invasion. Further, and in agreement with our previous findings, we also observed that overexpression of epsins led to epithelial cell migration beyond colony boundaries. Additionally, our results show that epsin-3 is the most potent paralog enhancing cell migration and invasion. Interestingly, epsin-3 expression is not widespread but highly restricted to migratory keratinocytes and aggressive carcinomas. Upon further investigation, we also identified epsin-3 as being expressed in pancreatic cancer cells. These findings suggest that upregulation of the EPN3 gene is specifically associated with invasive, aggressive cancers. We predict that investigation of these links between the endocytic machinery and mechanisms involved in tumor dissemination will contribute to the development of novel anti-metastatic and anti-cancer strategies.

The Epsin Family of Endocytic Adaptors Promote Cancer Cell Invasion

It is widely accepted that functional abnormalities in the endocytic machinery can lead to the onset of malignant transformation. In its most straightforward interpretation, lack of function of endocytic proteins would lead to deficient endocytosis and therefore to prolonged signaling from activated receptors. Interestingly, downregulation of the expression levels of endocytic proteins such as Dab2, Numb and POB1 have been observed in several cancers including ovarian, prostate and breast cancer. Another mechanism by which abnormal endocytic protein function can lead to carcinogenesis is through the generation of aberrant fusion proteins. For example, chromosomal translocations involving the CALM (Clathrin Assembly Lymphoid Myeloid leukemia) and AF10 (ALL1 Fused 10) genes produce a fusion protein implicated in acute leukemia.

Nevertheless, there are several examples of endocytic proteins upregulated in cancer. For example, elevated levels of epsins have been reported to be augmented in skin, breast and lung cancer. Additionally, intersectin has been shown to induce fibroblast transformation in vitro. Interestingly, both endocytic proteins have been directly implicated in the activation of Rho GTPase signaling pathways. Specifically, whereas the intersectin-L isoform has intrinsic Cdc42 GEF activity, epsins bind and inhibit the function of GAPs for Cdc42 and Rac1. Although it is not completely clear if amplified RhoGTPase signaling is sufficient to induce malignant transformation, it is predicted to enhance the dissemination of cancer. Indeed, we have demonstrated that the epsin family of endocytic adaptors is required for cell migration and that this function depends on the interaction of these proteins with the Cdc42/Rac1 GAP and Ral effector RalBP1. Further, our studies indicate that epsin-RalBP1 complex formation is required for proper Rac1 signaling. RalBP1 has been observed to be highly upregulated in several invasive cancers including bladder, lung, prostate and...
Additional epsin-dependent mechanisms for the enhancement of cancer cell invasion. Although our data indicate that the ability of epsin to affect cell invasion is mediated by its interaction with RalBP1 and the resulting RhoGTPase activation,13 we cannot discard additional contributions by other mechanisms. Indeed, endocytosis itself has been proposed to play an important role during cell migration. Thus, defects in the function of endocytic proteins such as Dab2, ARH, Numb, AP2 and clathrin, have also been linked to abnormal cell migration due to defective integrin endocytosis.20-23 Additionally, epsin has been directly and specifically connected to the activation of the Notch signaling pathway24,25 which is known to be involved in cell migration/invasion.26 In Drosophila, epsin is the only endocytic adaptor necessary for activation of Notch signaling in signal sending cells, likely due to its special ability to internalize ubiquitinated Notch-ligands.24,25 Further, this Notch-signaling activation...
function has been shown to be conserved in worms and mice. Nevertheless, this juxtacline cell-to-cell mechanism is unlikely to be involved in the epsin-mediated enhancement of fibrosarcoma cell migration and invasion. The epsilon-3 protein is expressed in all the cell types studied, and it has been shown that its expression is increased in response to growth factors. Therefore, function impairment of endocytosis is related to its capability of inducing migratory behavior.

Therefore, function impairment of endocytosis is related to its capability of inducing migratory behavior. Nevertheless, the contributions of epsin-mediated enhancement of cancer cell invasion due to endocytosis in general, and of Notch-ligands in particular, still needs to be assessed.

Cell sensitivity to anti-cancer drugs. Metastatic cells are usually associated with enhanced resistance to chemotherapy. Therefore, factors or pathways that contribute to migratory behavior are of high interest for therapeutic purposes. Given our recent findings, epsins might join the list of potential targets for anti-metastatic and anti-cancer strategies, which already includes their interaction partner RalBP1. In fact, it is tempting to speculate that in addition to other proposed mechanisms, RalBP1’s ability to promote cancer cell survival is related to its capability of inducing migratory behavior. Therefore, function impairment of endocytic proteins crucial to cell invasion (such as epsins and RalBP1) represents an exciting new direction for developing effective cancer therapeutics.

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