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Translational control of EMT by the Eukaryotic translation initiation factor 5A2 in cancer

Arantxa Martínez[1] , José Miguel Pardo[1] , Borja Belda[2] , Alihamze Fathinajafabadi[1] , Beatriz Pérez[1] , Carolina Gandía[1] , Jerónimo Forteza[3] , Alejandro Ferrando[2] , Rosa Farràs[1]

1) Centro de Investigación Príncipe Felipe, Valencia, Spain. 2) Instituto de Biología Molecular y Celular de Plantas, Consejo Superior de Investigaciones Científicas-Universitat Politècnica de València, Valencia, Spain. 3) Instituto Valenciano de Patología, Unidad Mixta de Patología Molecular. Centro Investigación Príncipe Felipe/Universidad Católica, Valencia, Spain.

It is estimated that metastasis is responsible for ~90% of cancer deaths. At the cellular level, epithelial to mesenchymal transition (EMT) is the initiating event in tumor metastasis. The basic hallmarks of EMT characteristic of tumor cells are the development of an invasive phenotype that requires loss of cell polarity, cytoskeleton reorganization and cell shape reprogramming to increase the motility of individual cells. How do cells orchestrate these morphological changes is poorly understood. eIF5A, a target of the polyamines, is a highly evolutionary conserved specific translation factor, and it is the only known protein that undergoes a post-translational modification that generates the hypusine residue, which is necessary for its activity. Overexpression of eIF5A isoform 2 is frequently observed in different cancer cell types including Non-Small Cell Lung Cancer (NSCLC) suggesting that aberrant expression of eIF5A2 may be responsible for the malignant behavior of cancer cells. The recent demonstration that eIF5A is required for the translation of proteins with consecutive Pro residues opens new avenues of exploring the existence of translation hubs. Studies of Gene Ontology have shown enrichment of polyproline rich proteins involved in the regulation of the actin cytoskeleton, with direct roles in cell morphology, migration and adhesion. Further characterization of proteins with polyproline segments also includes other proteins involved in the EMT. With this work, we hypothesize that aberrant expression of eIF5A isoform 2 conforms a translation hub for polyproline-rich proteins whose coordinated translation is crucial for cellular morphological alterations as those required for cancer progression and metastasis. Here we show that genetic inactivation of eIF5A2 in cancer cells results in the disorganization of actin cytoskeleton and inhibition of cell proliferation. Furthermore, we show that the activity of eIF5A2 is necessary for the complete epithelial-mesenchymal transition and for cell migration of lung cancer cells. The proposed work is directly relevant to cancer because EMT is a core mechanism underlying tumor metastasis. Modulation of the enzymatic activities by which EIF5A2 stability and function are controlled in the context of EMT will reveal candidate therapeutic targets for the prevention of metastasis of early-stage cancers. Downstream effectors of the EIF5A2 protein may also prove to be potential therapeutic targets, and will provide insight into the cellular mechanisms underlying EMT that may be translatable to a broad range of solid tumors.

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