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The adaptor protein Ruk/CIN85 is a novel key regulator of epithelial-mesenchymal plasticity in cancer cells and a potential therapeutic target

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For a long time, the genocentric paradigm of the etiology and pathogenesis of tumor diseases dominated in the field of molecular oncology. According to this paradigm, cancer is a genetic disease caused by the accumulation of somatic mutations that lead to a functional imbalance between tumor suppressor and oncogenic signals. Today, it is convincingly established that naturally occurring processes of dedifferentiation/transdifferentiation closely related to the phenomenon of cellular plasticity, play an important role in the control of cancer progression [1]. The biological program underlying all these processes involves the reciprocal transitions from epithelial to mesenchymal identity termed EMT/MET, while the ability of cells to undergo EMT is currently referred as epithelial-mesenchymal plasticity (EMP). EMT is coopted by cancer cells to acquire of a more aggressive tumor phenotype tightly interrelated with conversion of noninvasive tumor cells into stem-like states, increase of therapy resistance and metastatic potential. In addition, cancer cells, to increase their migratory and invasive potential, can acquire amoeboid features (MAT), as a more effective cellular state within EMT spectra [2].

Molecular strategies that orchestrate EMP include context-dependent dynamic changes in extracellular environment; consequent modulation of receptor-mediated signaling and metabolic networks; fine control of epigenetic events; control of gene and miRNA expression patterns, translation and post-translational modifications, which are realized in changes in the phenotype of cells and their biological responses.

The results of systemic studies obtained in the Department of Cell Signaling by using tumor cells of different tissue origins and *in vitro* and *in vivo* models demonstrated that the stable forced expression/down-regulation of SH3-containning adaptor protein Ruk/CIN85 is accompanied by activation/inhibition of signaling pathways that initiates global nuclear and metabolic reprogramming leading to EM-MA/AM-ME transitions depending on the optimal stoichiometry of Ruk/CIN85 in intracellular signaling complexes [3]. Taken together, the data obtained provide evidence to consider adaptor protein Ruk/CIN85 as a potent reprogramming factor that utilizes cellular plasticity to regulate the phenotype of tumor cells and may be useful for the development of new therapeutic approaches.

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