ERK activation globally downregulates miRNAs through phosphorylating exportin-5

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MicroRNAs (miRNA) are mostly downregulated in cancer. Systemic evaluation of miRNA has revealed that many pre-miRNA were retained in the nucleus of cancer cells. However, the mechanism underlying this phenomena and the precise consequence for tumorigenesis remains obscure. Here we showed that ERK suppresses pre-miRNA export from nucleus through phosphorylation of exportin-5 (XPO5) at T345/S416/S497. After phosphorylation by ERK, conformation of XPO5 is changed by prolyl isomerase Pin1, resulting in reduction of pre-miRNA loading. ERK also phosphorylates NUP153 to further inhibit pre-miRNA-XPO5 complex export. Globally miRNA downregulation was observed in liver cancer when XPO5 was phosphorylated, including the highly expressed miRNA, miR-122. Depletion of miR-122 increase SEPT9 expression to scaffold MAP4 and MARK4. Phosphorylated MAP4 detach from tubulin to increase microtubule dynamics, thereby inducing taxol resistance and tumorigenesis. Analysis of clinical specimens further showed that XPO5 phosphorylation is associated with poor prognosis for liver cancer patients. Our study reveals a novel function of ERK in miRNA biogenesis and suggests that modulation of miRNA export has potential clinical implications.