MtEF4 promotes tumorigenesis and metastasis in breast cancer via modulation of oxidative phosphorylation

Zhen Huang, Qianqian Chen, Yi Fang, Jing Wang, and Taotao Wei

MtEF4 expression on metastasis in the invasive cancer cells via a response in energy production and glycolysis compensatory.

MtEF4 enhances oxidative phosphorylation and mitochondrial biogenesis in invasive breast cancer cells by mediating mitochondrial protein synthesis. MtEF4 is commonly upregulated in breast tumors compared to patient-matched adjacent normal tissues, and is relevant with tumor progression. Down regulation of mtEF4 expression reduces ATP production, attenuates the formation of lamellipodia, inhibits mitochondrial OXPHOS, and results in impaired energy metabolism, which suppresses cell migration and invasion in vitro and in vivo. On the contrary, overexpression of mtEF4 elevates the mitochondrial respiration and cellular ATP level.

Introduction

Functional mitochondria are essential for the tumorigenesis and metastasis of cancer cells. Mitochondrial translation elongation factor 4 (mtEF4; also known as Guf1) is a key quality control factor in mitochondrial translation. Here, we investigate its function upon tumorigenesis and progression of breast cancer.

Results and conclusion

1. Human mtEF4 is overexpressed in breast cancer and subcellular localized in mitochondria

A. mtEF4 was highly detected in all tested cancer tissues, rather less in normal tissues. B. mtEF4 immunostaining was weaker in stage I cancer tissue sample than in stage II and III samples. C. Human mtEF4 was confirmed in various breast cancer cell lines. D. The location of mtEF4 to the mitochondria in MDA-MB-231 and 436 cell lines. And Δ1-49mtEF4 did exhibit observable local deficiencies.

2. mtEF4 expression facilitates mitochondrial morphology, redistribution and OXPHOS

A. Mitochondria gather around the nucleus in MDA-MB-231 (a) and 436 (b). MtEF4 protein levels (c). B. Relative OCR normalized in mtEF4 shRNA and scramble of MDA-MB-231, 436. C. Relative OCR normalized in mtEF4 over expression and vector control of MDA-MB-231, 436.

3. mtEF4 expression determines the migration and invasion in cells, and regulates the metastatic capacity in Nude Mice

A, B. mtEF4 shRNA and overexpression affected the migration and invasion abilities of MDA-MB-231 cells and 436 cells. C. Scramble and shRNA-mtEF4 pretreated MDA-MB-231 cells were injected into the tail vein of nude mice. After 12 weeks, metastatic nodules in lung surface. D. HE staining of C show tumor nodules. E. mtEF4 enhanced was associated with distant metastasis.

4. mtEF4 deficiency decreased ATP level, activities of mitochondrial respiratory complexes and impair the actin cytoskeletal assembly

A. ATP levels were decreased in shRNA-mtEF4 MDA-MB-231 and 436 cells. B. mtEF4 deficiency did not alter mtDNA content. C. The expression of NDUFA1, and NDUFA9 were downregulated in shRNA-mtEF4-pretreated cells. The expression of complex I – V were disturbed variously by downregulation of mtEF4. D. IGA analysis of mitochondrial respiratory complexes activities. E. ECR of scramble and shRNA-mtEF4 MDA-MB-231 cells. F. Immunofluorescence microscopy of positive MDA-MB-231 cells and 436 cells.

Focus on cellular metabolic function and carcinogenesis, especially the role of mitochondrial dysfunction in the development of hepatocellular carcinoma.

National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College
Zhen Huang
M.D Department of Hepatobiliary Surgery
Panjiayuannanli 17, Chaoyang District, Beijing 10021

E-mail: purage@163.com
Phone: +861087787100
Web: http://www.oicams.ac.cn