ERas (ES-cell expressed Ras) induces EMT and stem cell features in normal and tumorigenic human breast cells

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Abstract

Breast cancer is the most common cancer in women worldwide and it is the most frequent cause of cancer death in women [1]. This pathology is mainly classified based on hormone receptors and HER2 expression. Moreover, many genes (such as BRCA1, BRCA2 or TP53) are known drivers in mammary gland tumors. Despite these facts, the mechanisms of malignant progression and metastasis are not fully understood [2]. An important mechanism by which epithelial cells lose their cell polarity and cell-cell adhesion, and gain migratory and invasive properties is the epithelial-mesenchymal transition (EMT) process [3]. Ras family proteins are frequently mutated in human cancer but, interestingly, these mutations are rare in breast cancer [4]. Recently it has been reported that others member of this superfamily (such as R-Ras2) could be implicated in breast cancer. ERAS is a member of the small GTPase RAS protein family and it is constitutively active without mutation. However, this gene is expressed only in embryonic cells, but not in somatic cells [6]. Previously, ERAS has been shown to be involved in gastric cancer, neuroblastoma and melanoma [7-9]. We hypothesize that ERAS could be reactivated in breast cancer and promote malignant transformation and metastasis of breast cells. In order to understand the role of ERAS in mammary cells, we forced its expression in normal human mammary gland cells (MCF10A) and in a tumorigenic breast cell line (MDA-MB-231). We observed that MCF10A-ERAS presented morphological changes, being more fusiform, and loss of cell-substrate adhesion. ERAS was localized mainly in plasmatic membrane, although it is also found in cytoplasm and in other organelles. ERAs-expressing cells had higher proliferation rate and motility than control MCF10A cells and, furthermore, induced EMT resulting in increased levels of transcription factors involved in this process, loss of E-Cadherin and gain of N-Cadherin. Besides, the miRNA-200 family members (especially cluster II) and miRNA-205, which are relevant in EMT process, were downregulated. Moreover, cells expressing this gene lost EpCam expression, acquiring a mesenchymal phenotype, and underwent a large increase in $CD44^{high}/CD24^{low/-}$ population. In mammary gland, this subpopulation corresponds to stem cells, supporting that ERAS awards stem-like features. On the other hand, expression of ERAS gene in tumorigenic MDA-MB-231 cells gene generated larger, faster growth and more undifferentiated tumors than control cells. Taken together, these evidences support that ERAS may promote malignant progress in breast cells by activation of EMT and acquiring stem cells properties.

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