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Research paper

Systematic analyses of key genes and pathways in the development of invasive breast cancer

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ABSTRACT

Background: Ductal carcinoma in situ (DCIS) is a common type of non-invasive breast cancer and can sometimes progress into invasive breast cancer (IBC). Identification of the critical genes and biological processes specifically and/or commonly changed in DCIS or IBC can help us understand more about breast cancer development and provide more critical targets and signal transduction pathways for the diagnosis and treatments for breast cancer patients.
Aim and methods: We aimed to gain more understanding about the whole process of IBC development, especially in the early stage. Here we systematically analyzed an online breast cancer patient database to identify those significantly changed genes and biological processes in epithelium from normal stage to DCIS stage or from DCIS stage to IBC stage.
Results: 344 specific genes, such as FN1, AURKA and HSPA8, were found to be significantly changed (both upregulated and downregulated) in DCIS group in comparison with normal tissue group, which represents the gene profile changes in early stage of breast cancer development. Meanwhile, 304 specific genes were significantly changed (both upregulated and downregulated) in IBC group in comparison with normal tissue group, which represents the gene profile changes in late stage of breast cancer development. Importantly, seven genes were identified to have consistent changes in both early stage and late stage, indicating they might play "driving" roles in the breast cancer development. Of these 7 genes, 5 have been shown to be involved in breast cancer progression by previous studies, which demonstrates the validity of our analyses. Notably, DNAPTP3 was identified for the first time to play an oncogenic role in breast cancer development. In the GO term analyses, cell cycle genes was found to play more important roles in the early stage while biological adhesion was indicated to be more specifically involved in late stage of breast cancer development.
Significance: Our systematic analyses provide better understanding of the unique gene profiles and biological processes during the breast cancer development and identify more potentially important targets for future studies, such as DNAPTP3.

1. Introduction

Many cancers develop due to genetic dysregulation that leads to gene mutations and the altered cellular pathways. Breast cancer is one of the most commonly diagnosed cancers and its survival rate still hasn't made a significant improvement although there have been some improvements on the diagnosis and treatment. As the occurrence and development of breast cancer was mainly caused by the dysregulation of key genes (Kuo et al., 2012), better understanding of the genetic changes will benefit both the diagnosis and the treatment of breast cancer. For example, owing to the detection of the identified therapeutic

Abbreviations: DCIS, ductal carcinoma in situ; IBC, invasive breast cancer; GEO, Gene Expression Omnibus; DEGs, differentially expressed genes.

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Table 1
Statistical distribution of differentially expressed genes (DEGs) among these three comparisons.

	Comparison 1		Comparison 2		Comparison 3	
All |logFC| > 1 & adjusted p value < 0.01	485	259 (up) 226 (down)	648	342 (up) 306 (down)	173	77 (up) 96 (down)
Special |logFC| > 1 & adjusted p value < 0.01	71	48 (up) 23 (down)	457	277 (up) 180 (down)	127	62 (up) 65 (down)

genes and pathways in breast cancer research, the mortality rate for breast cancer is indeed reduced (Kourea et al., 2014). Therefore, more efforts are needed to investigate the mechanism of breast cancer development and to identify more clinical targets.

Based on the evidence from both clinical and molecular biological research, the occurrence of breast cancer has been considered as one linear multi-step process, which develops from normal epithelium into DCIS, then progresses to invasive breast cancer (IBC) and metastatic carcinoma (Espinoza et al., 2011; Prat et al., 2010). DCIS has been found to be a direct precursor to IBC and has its own characteristic pathological changes (Correa et al., 2009). In addition, DCIS has high recurrence after the localized radiotherapy and the endocrine therapies (Correa et al., 2009; Cuzick et al., 2011; Petrelli and Barni, 2011). However, our understanding of the molecular pathology of DCIS is still limited. There are numerous disputes on clinical treatment options for DCIS although some standardizations of the DCIS treatment strategies are recently carried out (Turashvili et al., 2007). Thus, more studies should be performed to investigate

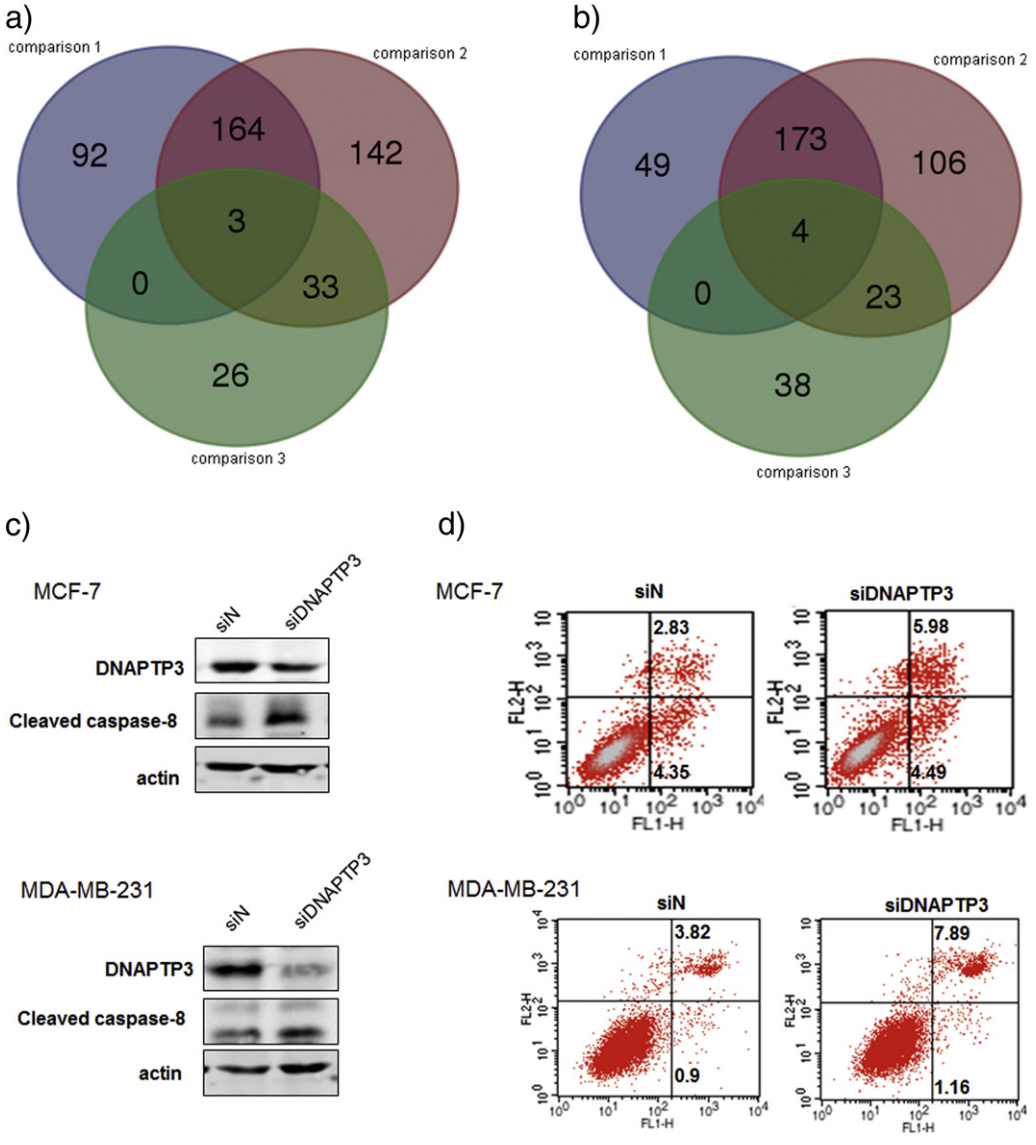

Fig. 1. Overlapping of the DEGs (differentially expressed genes) in different stages of breast cancer. A. Overlapping of the total number of up-regulated DEGs from three comparisons. B. Overlapping of the total number of down-regulated DEGs from three comparisons. Purple diagram was DEGs of Comparison 1 (DCIS samples vs normal samples), red diagram was Comparison 2 (IBC samples vs normal samples) and green diagram was Comparison 3 (IBC samples vs DCIS samples). C. Left panel: western blot was performed to show the knockdown efficiency of si*DNAPTP3* in breast cancer cells; right panel: flow cytometry analysis of Annexin V- (FL1-H) and PI- (FL2-H) labeled cells after knock-down of DNAPTP3 in breast cancer cells. D. MTT assay after knock-down of DNAPTP3 in breast cancer cells. E. Cell invasion assay after knock-down of DNAPTP3 in breast cancer cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)