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Original contribution

High expression of heat shock protein 10 correlates negatively with estrogen/progesterone receptor status and predicts poor prognosis in invasive ductal breast carcinoma☆,☆☆

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Summary Heat shock proteins (HSPs) usually are associated with stress response and tolerance. HSP10 is a co-chaperone for HSP60, which is involved in the mitochondrial protein-folding machinery. To the best of our knowledge, the expression of HSP10 in invasive ductal breast carcinoma (IDBC) has never been reported. In the present study, HSP10 expression in 242 cases of IDBC and 46 cases of noncancerous breast tissues was detected by immunohistochemistry staining. High expression was significantly more common in IDBC than in noncancerous breast tissues ($P < .001$). Also, high expression was significantly more common in poorly differentiated than in well- and moderately differentiated IDBC ($P = .023$). Furthermore, high expression correlated negatively with estrogen receptor and progesterone receptor expression ($P = .031$ and $P = .042$, respectively). The most interesting result of the study was that high expression of HSP10 was significantly associated with shorter overall survival by both univariate and multivariate analyses ($P = .013$ and $P = .036$, respectively). In conclusion, we report for the first time that high expression of HSP10 is negatively associated with estrogen receptor/progesterone receptor status and might be a novel independent biomarker for poor prognosis in IDBC.

1. Introduction

Invasive ductal breast carcinoma (IDBC) is the most common type of breast cancer, accounting for approximately 80% of such cancers. Further elucidation of the molecular mechanisms underlying IDBC is essential for the development of effective therapeutic agents and novel prognostic markers.

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Therefore, we focused on the chaperone system, heat shock proteins (HSPs). These are a group of proteins induced by exposure to a variety of stressors, such as heat shock, infection, inflammation, and so on [1]. Some of these HSPs also are present in unstressed cells and play an important role in correcting unfolded or misfolded proteins, so they maintain normal function in the cell. Thus, they have been termed *molecular chaperones*[2]. HSP10, which acts as a co-chaperone for HSP60 inside mitochondria, has been found in extramitochondrial sites as well and has different roles inside and outside the cell [3,4]. It is assumed that HSP60 is a proinflammatory factor [5]. In contrast, HSP10 is reported to have anti-inflammatory behavior in human monocytes [6]. HSP10 also localizes extracellularly during pregnancy, and extracellular HSP10 is often referred to as *early pregnancy factor* because it is released during the first stage of gestation and is involved in the establishment of pregnancy, in embryonic development, and in cell proliferation and differentiation [7]. The chaperonin system HSP10/60 assists in the folding of proteins in the cytosol, contributing to protein homeostasis, but it may also participate in a pathway that favors disease development rather than the opposite.

Moreover, a high concentration of HSP10 may activate the antiapoptotic Bcl-2 family to inhibit cell apoptosis, which benefits tumorigenesis [4]. Furthermore, the overexpression of HSP10 has been reported in a variety of tumors and nontumor lesions, such as those of the large intestine, ovary, liver, and prostate [8-11]. However, the expression of HSP10 and its clinicopathological/prognostic implications in IDBC have not been reported so far. In the present study, to investigate the role of HSP10 in IDBC, we constructed tissue arrays and detected the expression of HSP10 in IDBC by immunohistochemistry (IHC) staining. We also analyzed the relations between the expression of HSP10 and some of the clinicopathological characteristics and prognostic factors of IDBC.

2. Materials and methods

2.1. Clinical data

In this study, 242 cases of IDBC, all females, and 46 cases of noncancerous breast (control) tissues were selected randomly from the files of the Department of Pathology at the Second Xiangya Hospital of Central South University (Changsha, China). All patients with IDBC had been followed up, some for as long as 10 years, during the period from 2002 to 2012. These patients had been submitted to routine staging procedures and definitive surgical resection of the affected breast and axillary lymph nodes. All patients had a confirmed histologic diagnosis of IDBC according to the World Health Organization classification of breast cancers [12]. The staging was carried out according to the criteria of the seventh edition of the AJCC/UICC TNM Staging System [13]. Patients did not receive chemotherapy or radiotherapy before the operation, but all patients received standard postoperative adjuvant chemotherapy with or without radiotherapy according to their clinical stage. Complete clinical records and follow-up data were available for all patients. Written informed consent was obtained from these patients, and this study was approved by the Ethics Review Committee of the Second Xiangya Hospital of Central South University (approval number S-02-2000). Patient characteristics are listed in Table 1.

2.2. Construction and validation of tissue microarrays

Representative areas of IDBC and noncancerous breast tissue were marked on hematoxylin and eosin–stained slides and tissue paraffin blocks, and the marked areas of the blocks were sampled to construct the tissue microarrays (TMAs). The TMAs were assembled (Beecher Instruments, Silver Springs, MD) as described by Fan et al [14]. Two 0.6-mm tissue cores were taken from the paraffin block of each IDBC and control tissue. All tissue cores were distributed in 9 regular-size paraffin-receptive blocks, each containing 100 spots. A series of 5-μm-thick sections was obtained using a microtome, and the slides were covered with a thin paraffin film and stored at 4°C until used for IHC staining. All TMA specimens were valid for IHC analysis.

Table 1 Clinicopathological features of patients with IDBC and noncancerous breast tissues

Patient feature	No. of patients (%)
IDBC	
Age (y) [a]	
≤46	151 (62.4)
>46	91 (37.6)
Clinical stage	
I	19 (7.9)
II	107 (44.2)
III	85 (35.1)
IV	31 (12.8)
Lymph node status	
0	59 (24.4)
N1/N2/N3	183 (75.6)
Differentiation	
Well	16 (6.6)
Moderately	101 (41.7)
Poorly	125 (51.7)
Noncancerous breast tissues	
Age (y)	
≤46	29 (63.0)
>46	17 (37.0)

[a] The average age of all patients with IDBC was 46.2 years.