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Ductal carcinoma in situ of the breast: the importance of morphologic and molecular interactions☆

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Summary Ductal carcinoma in situ (DCIS) of the breast is a lesion characterized by significant heterogeneity, in terms of morphology, immunohistochemical staining, molecular signatures, and clinical expression. For some patients, surgical excision provides adequate treatment, but a subset of patients will experience recurrence of DCIS or progression to invasive ductal carcinoma (IDC). Recent years have seen extensive research aimed at identifying the molecular events that characterize the transition from normal epithelium to DCIS and IDC. Tumor epithelial cells, myoepithelial cells, and stromal cells undergo alterations in gene expression, which are most important in the early stages of breast carcinogenesis. Epigenetic modifications, such as DNA methylation, together with microRNA alterations, play a major role in these genetic events. In addition, tumor proliferation and invasion is facilitated by the lesional microenvironment, which includes stromal fibroblasts and macrophages that secrete growth factors and angiogenesis-promoting substances. Characterization of DCIS on a molecular level may better account for the heterogeneity of these lesions and how this manifests as differences in patient outcome and response to therapy. Molecular assays originally developed for assessing likelihood of recurrence in IDC are recently being applied to DCIS, with promising results. In the future, the classification of DCIS will likely incorporate molecular findings along with histologic and immunohistochemical features, allowing for personalized prognostic information and therapeutic options for patients with DCIS. This review summarizes current data regarding the molecular characterization of DCIS and discusses the potential clinical relevance.

1. Introduction

Ductal carcinoma in situ (DCIS) accounts for approximately 20% of all newly diagnosed breast cancer cases in the United States [1]. DCIS is defined as a neoplastic proliferation of epithelial cells with varying degrees of cytologic atypia that are confined to the mammary ductal-lobular system. DCIS itself does not result in

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mortality, and breast cancer–specific mortality among women with DCIS is extremely low, with 1.0% to 2.6% dying from invasive breast cancer (IBC) 8 to 10 years after a diagnosis of DCIS [2]. Because of the noninvasive nature and overall favorable prognosis of DCIS, a 2009 National Institutes of Health State-of-the-Science Conference issued a statement that advocated elimination of the term "carcinoma" in the name of this lesion [3]. Because DCIS is a nonobligate precursor of invasive ductal carcinoma (IDC), an invasive component is found in a subset of women who develop DCIS recurrence [4]. Furthermore, experimental data have shown that carcinoma precursor cells exist in DCIS lesions, suggesting that the aggressive phenotype of breast cancer is predetermined early at the premalignant stage [5].

Significant advances have been made in the diagnosis and therapy of patients with DCIS of the breast. Early detection has led to an increase in DCIS cases seen by pathologists in their daily practice. Although most women are treated by surgical excision followed by radiation therapy and anti-hormonal medications, a number of series have also demonstrated the natural course of untreated DCIS [4,6,7]. Although data demonstrate that there could be a population of patients who can safely undergo observation after a breast-conserving surgery, many physicians and patients are reticent to undergo this course of treatment for fear of recurrence [7,8]. Fifty percent of DCIS recurrence actually presents as an invasive cancer; therefore, consequences could be significant [9]. Thus, it is likely that a significant number of patients are being overtreated.

However, considering potential long-term adverse effects of radiation therapy, it seems prudent to identify a population of patients to observe without further therapy. Studies have shown that certain clinicopathological features of DCIS may be prognostic of local and/or invasive recurrence after surgical excision [6,7,10]. For instance, many studies have suggested that the tumor size is a strong predictor of local recurrence [7,11]. Nuclear grade and margin status are other factors that appear to influence recurrence in DCIS, although certainly there are studies that refute these findings [12]. Two major clinical tools that aid in risk stratification and treatment planning—the University of Southern California/Van Nuys Prognostic Index and the DCIS nomogram introduced by Rudloff et al—use both clinical and pathological factors such as tumor size, necrosis, and margin status [10,13,14]. Although our current ability to accurately predict recurrence on the basis of this parameters is limited, clearly the paradigm that "one approach fits all" in patients with DCIS is shifting. The current understanding is that DCIS is not one disease but a heterogeneous group of cancers with distinct morphologic, immunohistochemical, and biological features.

Recent research efforts have focused on classifying patients who may be managed conservatively and those who are at higher risk for disease progression and may require adjuvant therapy. The ideal classification scheme would be clinically useful and easy to adapt with the ability to stratify patients into prognostic groups. Although not consistently identified in all studies, certain histopathologic parameters such as lesion size, margin status, architectural pattern, nuclear grade, presence of comedo necrosis, and expression of various immunohistochemical markers have been variably shown to affect the risk of recurrence in premalignant breast lesions [12]. Improved molecular characterization of DCIS will offer additional, perhaps more definitive, prognostic information and may provide the opportunity for personalized therapeutic options for patients with DCIS.

2. DCIS carcinogenesis

There is a continuum of nonobligate precursor lesions to IDC, consisting of flat epithelial atypia, atypical ductal hyperplasia (ADH), and DCIS. Moreover, low-grade and high-grade DCISs likely arise from 2 distinct evolutionary pathways. Flat epithelial atypia is genetically related to ADH and is likely a precursor to ADH, which, in turn, is the precursor to low-grade DCIS [4,15].

The pathophysiology of the malignant transformation from DCIS to IDC has been studied at the molecular level. Comparative genomic hybridization studies of synchronous and metachronous DCIS and IDC lesions have revealed a near-identical pattern of genomic alterations, correlating with tumor grade, supporting a molecular continuum between DCIS and IDC. Specifically, low-grade lesions harbor frequent loss of 16q and 17p, whereas high-grade lesions have complex genomic alterations including 13q loss and high-level amplifications of 17q12 and 11q13 [16]. The use of gene expression microarray technology has further refined our knowledge of DCIS as a heterogeneous disease and has provided a new classification based on molecular signatures. Ma et al [17] discovered that unique gene expression signatures are associated with different tumor grades, irrespective of tumor stage. ADH, low-grade DCIS, and low-grade IDC share a near-identical gene expression profile consisting of genes associated with the estrogen receptor (ER) phenotype, whereas both high-grade DCIS and high-grade IDC possess a unique gene expression profile consisting of genes associated with mitotic activity and cell cycle processes. In addition, these authors identified a subset of genes with quantitative expression levels that correlate with advanced tumor grade and with the transition from DCIS to IDC. This suggests that the transcriptional program that drives cancer cells to an advanced tumor grade may also confer invasiveness. Specifically, the gene ribonucleotide reductase M2 (*RRM2*) may play a dual role in both supporting rapid cell proliferation and promoting invasive growth behavior [17]. In the transition to invasive disease, low-grade DCIS lesions give rise to well-differentiated IDC after a long latency period, and high-grade DCIS lesions give rise to poorly differentiated IDC after a relatively shorter period [18]. Using a supervised classification, Hannemann