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Low-Grade and High-Grade Invasive Ductal Carcinomas of the Breast Follow Divergent routes of Progression

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ABSTRACT Low-grade invasive ductal carcinoma is almost diploid, and has frequent losses of chromosome 16q, which is shared by other precancerous lesions of the mammary gland such as flat epithelial atypia (FEA), atypical ductal hyperplasia (ADH), and low-nuclear grade ductal carcinoma in situ (DCIS). The genetic alterations accumulate in a stepwise fashion as the precancerous lesions progress to invasve ductal carcinoma. This supports the linear progression model of breast cancer from FEA, through ADH, to low-nuclear grade DCIS as non-obligate early events in low-grade IDC evolution. In contrast, high-grade carcinoma tends to aneuploidy with complex genetic alterations—most importantly, frequent gains at chromosome 16q. Frequent losses at chromosome 16q in low-grade IDC and gains in the same arm of the same chromosome in high-grade IDC imply that these lesions are two end outcomes of different disease processes and that they do not lie in the same continuum of a process. Therefore, low-grade and high-grade IDC are two distinct diseases with a divergent route of progression.

KEY WORDS: flat epithelial atypia, atypical ductal hyperplasia, ductal carcinoma in situ, invasive ductal carcinoma, histologic grade, breast cancer progression.

Introduction

Breast cancer is the most common cause of cancer-related deaths in women[1]. It is a heterogeneous disease at the clinical, morphological, and molecular levels[2,3]. The evolution of the disease is incompletely understood and hence it is difficult to predict its progression. Early detection and treatment of the disease remains the most important way of decreasing its incidence and mortality, and of improving the quality of lives of patients. In the USA, overall, breast cancer incidence rates have levelled off since 1990, with a decreasing trend in the period from 2001 to 2006. The mortality attributed to the same disease has also been decreasing significantly since the early 1990s[4]. This improvement is attributed mainly to early detection of the disease, and more efficacious therapeutic options developed in the last three decades[5,6]. Owing to the high incidence of invasive breast cancer and the limited success in improving cure rates, a growing interest has developed in the detection and understanding of precursor lesions[7]. Understanding the behaviour and predicting the progression of precursor lesions of invasive breast cancer depends on understanding of their biologic features in terms of alterations at the genomic and transcriptomic levels as demonstrated by losses or gains at specific chromosomal loci.

Histologic grading of invasive ductal carcinomas (IDCs) is closely correlated with the clinical behaviours of the tumors[8–10]. Consequently, early molecular studies of IDCs focused on the relationship between tumor genomic alterations and tumor grade. Such comparisons have contributed significantly to the understanding of breast cancer progression[8,11,12]. This understanding has improved even more in the past couple of decades as a result of advances in microdissection, cellular purification and high throughput microgenomic technology. Earlier information on breast cancer and its precursor lesions, which was based on epidemiologic, morphologic, and immunohistochemical methods, is being reshaped and refined by the molecular diagnostic methods[12]. Progress in molecular methods is amassing evidences showing that the traditional linear model of progression of breast cancer is an oversimplification of a more complicated process[3].

Here, we present an overview of the histomorphologic patterns and molecular alterations of low-grade and high-grade IDCs and also some discrete precancerous lesions (flat epithelial atypia (FEA), atypical ductal hyperplasia (ADH), and ductal carcinoma in situ (DCIS). We present the histomorphologic features, expression profiles, and important genetic aberrations of low-grade and high-grade IDCs of no special type (NST) and some of the discrete precancerous lesions.

Precursor lesions of the breast

Observational morphological and molecular studies have demonstrated that some precancerous breast lesions sharing the same types of genetic aberrations exist synchronously or meta-synchronously with IDCs. The associations of these lesions with IDCs cannot be explained as occurring just by chance. FEA, ADH, and low-nuclear grade DCIS share the same immunoprofiles and genetic aberrations. In contrast, high-nuclear grade DCIS and high-grade IDCs have complex genetic alterations, which implies that the former is a non-obligate precursor lesion of the latter[13,14].

Flat epithelial atypia (FEA): earliest identifiable clonal lesion

FEA is the earliest identifiable clonal lesion, characterized by replacement of the normal native luminal layer by cells having various degrees of atypia. Most importantly, the lesion has cytological abnormalities rather than architectural abnormalities, which may be missed in a histopathologic evaluation with low-power magnification. Intraluminal proliferations are rarely, if ever, found[15,16] and, if they are found, comprise no more than tufts or bridges.

FEA is positive for both estrogen and progesterone receptors, does not overexpress Her-2 and lacks basal markers[14]. Moinfar et al. described the clonal nature of this lesion and found loss of heterozygosity (LOH) in pure FEA lesions and FEA lesions associated with DCIS or IDC at different loci of the chromosomes[15]. The most common genetic alterations were found to be at chromosomes 11q, 16q, and 3p in 50%, 45%, and 41% of cases, respectively. Others have documented chromosomal losses, LOH, and allelic imbalance on 1p, 3p, 5q, 9p, 9q, 10q, 11q, 12q, 16q, 17p, 17q, 18p, 21q, and 22q; and gains on 7q, 11q, 15q, 16p, 17q, 19q[14–17].

Atypical ductal hyperplasia (ADH): diagnosis of exclusion

ADH is a lesion with some, but not all, of the histologic and cytologic features of DCIS. It is, therefore, a diagnosis of exclusion. ADH is most commonly detected incidentally and in association with screen-detected benign microcalcification. It is found in only 4% of symptomatic benign biopsies[18,19]. The difficulty in diagnosing ADH is mainly in distinguishing it from low-grade variants of DCIS. Histomorphologic diagnosis of ADH is based on both a qualitative and quantitative assessment of the lesion. The qualitative assessment is based on logical features and architectural growth patterns. Qualitative features such as evenly distributed uniform monomorphic luminal epithelial cell population with nuclear hyperchromasia which are immunoreactive to CK 8, 18, and 19 characterize ADH[18,20]. Quantitatively, the size of the lesion is usually small and barely exceeds 2–3 mm. Proliferations with high-grade cytology (with or without necrosis) qualify as DCIS, regardless of the size or quantity of epithelial proliferation. The diagnosis of ADH is made only in those cases in which a diagnosis of DCIS is seriously considered but where the architectural, cytologic and quantitative features do not amount to a confident diagnosis of DCIS[18].

ADH lesions are hormone receptor positive but do not overexpress Her-2. Additionally, these lesions do not express basal markers. Their features are similar to that of low-nuclear grade ductal carcinoma in situ and luminal A subtype of IDCs NST[14,21,22].

About fifty per cent of ADH cases share their LOH patterns with invasive carcinomas from the same breast[23]. Several studies have documented chromosomal alterations, LOH, and allelic imbalance on 1q, 3p, 8p, 9p, 11q, 11p, 13q, 14q, 16q, 17q, 17p, 20p, 21q, Xp and gains on 1p, 1q, 2q, 3p, 8q, 10p, 11q, 15q, 17q, 20q, 20p, 22q, Xp, 16p[23–27].

Ductal carcinoma in situ (DCIS): membrane-bound malignant cells

DCIS is an intraductal proliferation of malignant epithelial cells without evidence of invasion of the surrounding stroma across the basement membrane. It is a unicenteric disease as shown by studies from three-dimensional reconstruction models. Pure DCIS accounts for 15%–20% of the breast carcinoma diagnosed in developed countries compared with 5% before the advent of the screening program[18,20].

The National Coordinating Group for Breast Cancer Screening Pathology in the UK recommends use of cytonuclear features for subdividing DCIS in to three

grades[18]: high-, low- and intermediate-nuclear grades. This grading system is widely accepted. This cytonuclear grading reflects the behavior of the lesions and also suggests the possibility of genetic alterations within the lesions[28].

Low-grade DCIS is composed of small monomorphic cells with monotonous small nuclei (may be larger than adjacent normal epithelial cells) which have a regular chromatin pattern. Nucleoli are inconspicuous and mitotic figures are rare. This lesion frequently has cribriform or micropapillary configurations, which usually coexist. Other architectural features are growth in arcades and solid patterns. High-nuclear grade DCIS is composed of highly atypical pleomorphic cells. Nuclei are markedly pleomorphic, poorly polarized, with irregular contour and distribution, course clumped chromatin, and prominent nucleoli. Mitotic figures are common. Architectural patterns may be variable and include micropapillae, cribriform, and solid configurations. Central necrosis may be apparent, with or without calcifications. Intermediate-nuclear grade DCIS lesions comprise cells with cytonuclear features intermediate between the high-grade and low-grade DCIS lesions[18,20,29].

Low-nuclear grade DCIS are generally hormone receptor positive and do not overexpress Her-2 receptor[29]. Various molecular studies have shown that low-nuclear grade DCIS lesions are diploid/near diploid whereas high-nuclear grade DCIS lesions show aneuploidy[14]. Different studies of chromosomal aberrations and genetic analysis have shown losses, LOH, and allelic imbalances on 2p, 6q, 8p, 9p, 11p, 11q, 13q, 14q, 16q, 17p, 17q, and gains on 1q, 16p, 20q, 22q,17q[14,23,24,27,30].

The immunohistochemical profiles and genetic aberrations of high-nuclear grade DCIS are more heterogeneous and complex than those of low-nuclear grade DCIS lesions[14,21,29]. The chromosomal aberrations, LOH, and allelic imbalances observed in high-nuclear grade DCIS are on 2q, 6q, 8p, 9p, 11p, 11q, 13q, 14q, 16q, 17p, 17q, 4q, 5q, 1p, 12q, 16q, 22q and gains on 1p, 1q, 2q, 5p, 6p, 6q, 7q, 8q, 9q, 10q, 12q, 14q, 15q, 16p, 17q, 19q, 20q, 21q, 22q[14,23,24,27,30]. Despite the complexity of genetic aberrations and heterogeneity of high-nuclear grade DCIS, deletions of the whole arm of 16q occur in a small proportion of such lesions, as is also the case for high-grade IDCs. In contrast, a gain of 16q is an uncommon event in FEA, ADH, and low-grade IDCs[14,30].

Invasive ductal carcinoma (IDC)

IDCs are histomorphologically subdivided according to their patterns of growth and degrees of differentiation[8]. About 60%–75% of all breast cancers are accounted for by IDCs NST. These are ductal carcinomas without specific histologic features or with specific features comprising <50% of the tumor size. The special histologic variants of IDC include tubular, cribriform, mucinous, medullary, etc. We will restrict our discussion to IDCs NST[31].

Histomorphologic features of IDCs NST vary considerably. The regularity of defined structures that is associated with ductal carcinomas of specific types is absent. The cytologic and architectural appearance of the tumor has a wide range. The cytoplasmic and nuclear appearance ranges from regular and uniform features to a highly pleomorphic form. Nucleoli may be prominent and multiple and the mitotic activity may be virtually absent or extensive. Architecturally, the tumor cells may be arranged in cords, clusters and trabeculae while some tumors are characterized by a predominantly solid or syncytial infiltrative pattern with little associated stroma. Glandular differentiation as tubular structures with central lumina may be apparent in a proportion of tumors. The Nottingham Grading System subdivides breast cancer into histologic grades according to the degree of differentiation. Semi quantitative evaluations of tubule (gland) formation, nuclear pleomorphism, and mitotic count are used to assess the level of differentiation of IDCs and subdivide them in to high, low, and intermediate grades[11,31].

Multiple independent studies have shown that the histologic grade has a prognostic value that is at least equivalent to the status of lymph node metastasis and better than that of tumor size[14]. The size, nature, metastasis, and recurrence of breast cancers are closely related to the grade of the tumor[10,14]. In general, low-grade tumors are associated with relatively more favorable outcomes than high-grade tumors. Moreover, tumors of different histological grades show distinct molecular profiles at the genomic, transcriptomic and immunohistochemical levels. Hence, histologic grade reflects the genomic make up of breast cancers[14,32]. The molecular phenotypes of breast cancer described by Perou and colleagues[33], more than a decade ago, are also reflected in the grades of the tumors. Luminal subtypes of breast cancer (estrogen receptor positive tumors) are commonly low tumors, which are candidates for endocrine therapy. These tumors have a favorable course and good prognosis. Tumor subtypes which overexpress Her-2 and are triple negative are generally high-grade tumors, characterized by an aggressive nature, early metastasis, and a high rate of recurrence[14]. Intermediate-grade tumors show features of both high- and low-grade tumors.

With the advent of molecular methods of investigation, it has become apparent that histologic grades are closely associated with the type, pattern, and complexity of numerical chromosomal aberrations. Low-grade IDCs NST are almost diploid and are characterized by frequent loss on 16q in 85% of cases. Other chromosomal aberrations in low-grade IDCs include gains on 1q, 16p and 8q. On the other hand, high-grade tumors show aneuploidy with a high frequency of complex genetic alterations. The genetic alterations in high-grade IDCs include, but are not limited to, loss on 1p, 5q, 8p, 11q, 13q, 14q, 17p and gains on 1q, 5p, 8q, 17q, and 20q. Amplifications occur on 1q, 6q22, 8q22, 11q13, 17q12, 17q22–24, and 20q13[3,34–36]. Loss on 16q in low-grade IDCs and gains in the same arm of the same chromosome in high-grade IDCs are the most common recurring genetic alterations, among others[12,30,36]. However, <20% of high-grade tumors have a loss on chromosome 16q. Some evidence suggests that the mechanism of loss in this case differs from that of low-grade IDCs[3,14]. Additionally,

high-grade IDCs which have a loss at 16q belong to the luminal subtype of IDCs NST. The different patterns of chromosomal aberrations for low-grade and high-grade IDCs suggest that they are two different diseases with different routes of progression. This evidence implies that progression of low-grade IDCs to high-grade IDCs is uncommon and an unlikely biologic phenomenon[3,12,14].

Intermediate-grade IDCs display a combination of low-grade and high-grade genomic alterations, suggesting that this group of tumors consists of a mixture of 'low-grade-like' and 'high-grade-like' IDCs.

Divergent routes of progression of high-grade and low-grade IDCs

It is, now, abundantly clear that breast cancer is not a single disease. It is a collection of multiple diseases that affect the same organ structure. Histopathologic studies, immunoprofiling, and gene expression profiles provide ample information about the nature of breast cancer[14]. Generally speaking, the different grades of IDCs are composed of tumors with different immunophenotypes. Low-grade IDCs, for instance, are commonly estrogen receptor positive while high-grade tumors are estrogen receptor negative. Each immunophenotype has a genetic alteration that characterizes the nature and behavior of the tumor.

Garcia et al. and other investigators hypothesized that breast cancer progression could be broadly classified into two groups based on histologic grade: low-grade and high-grade routes of progression[3,14]. Immunoprofiles and molecular evidence corroborates this hypothesis. The low-grade route consists of a family of lesions that are generally described as low-grade neoplasia, including but not limited to FEA, ADH, low-nuclear grade DCIS, and low-grade IDCs NST[14]. These lesions display hormone receptors, lack Her-2 overexpression and expression of basal markers. They have a simple, diploid/near-diploid karyotype, and display frequent deletions of 16q ($>$ 80%), and gains of 1q ($>$ 75%) and 16p (50%)[3,14,35–37]. In contrast, the high-grade route of progression includes high-nuclear grade DCIS and high-grade IDCs NST. These high-grade lesions are more heterogeneous and complex and can be classified by microarray expression profiling as luminal B, Her-2 type or triple-negative phenotypes. Comparison of lesions in this family taken as a group with those in the low-grade family, shows that they (*a*) lack hormone expression; (*b*) overexpress Her-2; (*c*) express basal markers; (*d*) have a higher prevalence of aneuploidy, complex karyotype, numerous unbalanced numerical changes mapping to several chromosomal arms. The most common chromosomal aberrations are loss of 1p, 8p, 17p, and gains of 1q and 8q. Amplifications are commonly observed at 1q, 8q, 17q, and 20q chromosomal arms[14,38]. However, $<$ 20% of high-grade lesions lose the whole 16q, which is the typical characteristic chromosomal aberration of the low-grade family of neoplasia. There is evidence that the mechanism that leads to loss of 16q in high-grade lesions is different from that of the low-grade family of lesions. Moreover, high-grade lesions with loss of whole 16q are hormone receptor positive and do not overexpress Her-2. These tumors might have progressed from the low-grade family of neoplasia[3,14].

In conclusion, it can be stated that histopathologic, immunoprofile and molecular evidences indicate divergent route of progressions for high-grade and low-grade IDCs. And the progression of low-grade IDCs to high-grade IDCs is an uncommon biologic phenomenon. Meticulous histopathologic evaluation and careful grading of a tumor provides inexpensive and validated information which helps in the choice of therapeutic regimen and in assessing patient prognosis.

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Conflict of interest statement

No potential conflicts of interest were disclosed.

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