How to personalise treatment in early breast cancer

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Breast cancer is thought to develop through multiple stages from premalignant atypical hyperplastic lesions, to carcinoma in situ (ductal and lobular), to invasive carcinoma, and eventually, to metastatic disease [1]. In such a progressive continuum, early breast cancer would include in situ lesions as well as small, often non-palpable, invasive lesions. This lecture will focus on lesions of the ductal type as these constitute the majority of the diagnosed cases.

Ductal carcinoma in situ (DCIS) is a proliferation of apparently malignant cells within the lumen of the mammary duct that have not penetrated the myoepithelial basement membrane. DCIS is a common diagnosis in women undergoing screening mammography; the incidence has increased over recent decades and accounts for about 20–25% of newly diagnosed cases [2,3]. DCIS is a highly heterogeneous disease and as the natural history of these lesions is not known, the majority of patients are treated with surgery with or without adjuvant therapy. Local recurrence rates are reduced by surgical treatment, though breast cancer-specific survival is not improved. However, mortality from invasive breast cancer is extremely low among patients with DCIS within 10–12 years following diagnosis [4]. It is unknown whether this is solely due to the benign nature of most in situ lesions or also due to effective treatment regimes. Due to a lack of good prognostic markers, women who would never experience invasive disease are undergoing potentially harmful treatment. Current treatment for DCIS includes radiotherapy, endocrine treatment and sentinel lymph node biopsy. A more thorough understanding of the clinical behaviour and the biology of the early stages of breast cancer and the transition to invasive cancer is needed to be able to differentiate between the benign and more aggressive cases and thereby be able to design appropriate treatment for the individual patient.

Molecular studies have generated support for the hypothesis that the invasive phenotype of breast cancer is determined at the pre-invasive stages. Whether progression of DCIS occurs linearly from low grade to high grade DCIS and subsequentially to invasive cancer, or that the grade of DCIS corresponds to the grade of a subsequent invasive cancer, is somewhat debated. However, molecular evidence accumulated over the last few years using whole genome technologies has led many investigators to suggest that breast cancer develops along two distinct genetic pathways that correlate with nuclear grade.

A pertinent question relates to the malignant nature of DCIS and whether the cells of these pre-invasive lesions are indeed malignant [5]. Despite the relevance of this issue, several reports show that carcinoma cells within these lesions exhibit numerous genetic and epigenetic aberrations and indicate that the invasive phenotype is predetermined at an early stage of breast cancer progression. For example, numerous specific molecular aberrations have been detected in the early stages, including atypical ductal hyperplasia (ADH). Some of the earliest changes in tumour development are gene expression changes caused by methylation of tumour-related genes. Methylation events typically increase from ADH to DCIS, but are qualitatively similar between DCIS and invasive cancer. Genomic alterations such as loss of 16q have been observed in lower grade DCIS and several, more complex rearrangements have been detected in high-grade DCIS. Similar patterns of genomic aberrations are observed in DCIS lesions and in adjacent invasive cancer indicating a direct relationship between DCIS and invasive carcinoma (reviewed in Bombonati and Sgroi [6]). Hence, DCIS is heterogeneous, similar to invasive carcinoma and the molecular subtypes of breast cancer originally defined for invasive breast cancer have also been identified in DCIS. Furthermore, and independent of the subtypes, a small subset of DCIS lesions displaying a distinct gene expression pattern indicative of an invasive potential have been identified, demonstrating that aggressiveness is genetically programmed at an early stage [7].

Tumour growth is dependent on interactions between the epithelial cells and the dynamic microenvironment in which they reside. Molecular changes in the cells of the microenvironment of early lesions have been observed and these may both precede and be a consequence of changes in the epithelial cells.

Specific gene classes are found altered in tumour stroma during breast cancer progression, such as genes encoding components of the extracellular matrix and factors involved in matrix remodelling. The intraductal microenviroment is hypoxic and nutrient-deprived and DCIS cells must adapt to these conditions in order to survive and invade through the basement membrane. This adaptation may be facilitated in the presence of specific genetic aberrations that promote tumour progression [8].

In summary, genome-wide studies have helped in the mapping of different types of molecular alterations in early breast cancer as well as in invasive cancer, providing a valuable atlas for identifying specific changes and molecular events that may serve as markers of invasion and progression. Together with studies of the tumour–stroma interactions to identify which and how survival pathways are activated for pre-malignant cells to be able to invade surrounding tissue, this will help us in understanding more of when invasion occurs and what the triggering events are. Such knowledge can be exploited for therapeutic purposes and possibly to treat the cancer before it becomes invasive.

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References

1 Allred DC, Mohsin SK, Fuqua, SA. Histological and biological evolution of human premalignant breast disease. *Endocr Relat Cancer* 2001;**8**:47–61.
2 Hofvind S, Vacek PM, Skelly J, Weaver DL, Geller BM. Comparing screening mammography for early breast cancer detection in Vermont and Norway. *J Natl Cancer Inst* 2008;**100**:1082–91.
3 Ernster VL, Ballard-Barbash R, Barlow WE, et al. Detection of ductal carcinoma in situ in women undergoing screening mammography. *J Natl Cancer Inst* 2002;**94**:1546–54.
4 Ernster VL, Barclay J, Kerlikowske K, Wilkie H, Ballard-Barbash R. Mortality among women with ductal carcinoma in situ of the breast in the population-based surveillance, epidemiology and end results program. *Arch Intern Med* 2000;**160**:953–8.
5 Allegra CJ, Aberle DR, Ganschow P, et al. NIH state-of-the-science conference statement: diagnosis and management of ductal carcinoma in situ (DCIS). *NIH Consens State Sci Statements* 2009;**26**:1–27.
6 Bombonati A, Sgroi DC. The molecular pathology of breast cancer progression. *J Pathol* 2011;**223**:307–17.
7 Muggerud AA, Hallett M, Johnsen H, et al. Molecular diversity in ductal carcinoma in situ (DCIS) and early invasive breast cancer. *Mol Oncol* 2010;**4**:357–68.
8 Espina V, Liotta LA. What is the malignant nature of human ductal carcinoma in situ? *Nat Rev Cancer* 2011;**11**:68–75.