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Chapter 4

Early-Stage Progression of Breast Cancer

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Abstract

Breast cancer can be defined as a group of diseases with heterogeneous origins, molecular profiles and behaviors characterized by uncontrolled proliferation of cells within the mammary tissue. Around one in eight women in the US will develop breast cancer in their lifetime, making it the second most frequently diagnosed cancer behind skin cancer [1]. In 2015, an estimated 231,840 cases of invasive carcinoma were diagnosed, and over 40,000 deaths were caused by breast cancer which accounts for almost 7% of all cancer mortality each year [1, 2]. In 2015, 60,290 cases of in situ breast cancer were diagnosed, representing over 14% of all new cancer cases among women and men [1]. The steep increase in diagnosis of early-stage breast cancer over the past 10 years is believed to be a result of more frequent mammography. However, since over half of these in situ lesions will not progress to invasive breast cancer, controversies have arisen about approaches to treatment and prevention of progression of early-stage in situ breast cancer. Understanding the mechanisms of transition of normal breast to in situ pre-neoplastic lesions and invasive breast cancer is currently a major focus of breast cancer research with implications for preventive and clinical management of breast cancer. In this review, we give an overview of current knowledge on the molecular and pathological changes that occur during early-stage progression of breast cancer and describe some of the current models that are used to study this process.

Keywords: ductal carcinoma in situ, molecular and cellular drivers of invasive progression, early-stage breast cancer models

1. Pathophysiology of breast cancer

1.1. Anatomy and histology of the normal mammary gland

Within each mammary gland, there are 15–20 lobes containing 20–40 smaller compartments called lobules. Each lobule is composed of 10–100 grapelike clusters of milk-secreting...
glands termed acini, which are connected to lactiferous ducts [3]. The epithelium throughout the acini and ducts consists of two layers: an inner layer of polarized and cuboidal luminal cells that encapsulate a central lumen, and a basal outer layer of myoepithelial cells with contractile properties conferring these cells an active role in the milk excretion during lactation [3, 4]. Myoepithelial cells also ensure the maintenance of the adjacent luminal epithelial cell polarity and the synthesis of a laminin-rich basement membrane (BM) that forms a structural barrier separating the glandular epithelium from the stroma [5]. In the normal mammary gland, luminal epithelial cells are characterized by the expression of the luminal cytokeratins CK7, CK8 and CK18, sialomucin, epithelial-specific antigen, occludin and integrin [4] [5, 6]. On the other hand, myoepithelial cells express the basal cytokeratins CK5, CK14 and CK17 along with CD10/CALLA, alpha-smooth actin and P63 [6, 7]. The stroma surrounding the mammary gland consists of an insoluble extracellular matrix (laminin, fibronectin, collagen, proteoglycans), mesenchymal cells (fibroblasts, adipocytes, endothelial cells and resident immune cells), and various growth factors and cytokines [8]. Aberrant interactions between mammary epithelial cells and the stroma may lead to structural and functional alterations of the mammary gland biology and ultimately promote breast malignancy [8].

1.2. Hyperplasia/atypical hyperplasia and “in situ” carcinoma histopathology

Many suspicious mammograms or palpable findings turn out to be benign lesions following breast biopsy [9]. However, based on the histopathological report and family history, about 3–10% of these benign lesions are considered to be at high risk of later breast cancer and are referred to as atypical hyperplasia [10, 11]. Atypical hyperplasia is a premalignant lesion diagnosed based on the architectural pattern, cytology and the disease extent and is traditionally classified into two subtypes: atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) [12]. The absolute risk of developing breast cancer has been estimated at about 30% for women diagnosed with atypical hyperplasia after 25 years of follow-up [13].

“In Situ” carcinoma, also known as stage 0 breast cancer, is defined by the clonal proliferation of neoplastic epithelial cells within the ducts (e.g., ductal carcinoma in situ) or the lobules (e.g., lobular carcinoma In Situ) of the mammary gland. “In Situ” means that cancer epithelial cells remain confined inside the mammary ducts or lobules with no evidence of cancer cell invasion into the surrounding stroma [1]. Ductal carcinoma in situ (DCIS) incidence has risen, and it accounts for 15–20% of the breast cancer currently diagnosed as a result of increased screening mammography in the past 30 years [14, 15].

Even if DCIS is not immediately life-threatening, 14–53% of untreated DCIS lesions will progress to invasive ductal carcinoma (IDC) with considerable inconsistency in the timing and nature of this transition [16–20]. The most widely accepted model of breast carcinogenesis is the model of “linear” progression that hypothesizes that DCIS is an obligate precursor of IDC evolving through sequential stages, dependent upon early genetic and/or epigenetic changes [21–26].
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