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Review

Brain metastasization of breast cancer

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ABSTRACT

Central nervous system metastases have been reported in 15–25% of breast cancer patients, and the incidence is increasing. Moreover, the survival of these patients is generally poor, with reports of a 1-year survival rate of 20%. Therefore, a better knowledge about the determinants of brain metastasization is essential for the improvement of the clinical outcomes. Here, we summarize the current data about the metastatic cascade, ranging from the output of cancer cells from the primary tumour to their colonization in the brain, which involves the epithelial-mesenchymal transition, invasion of mammary tissue, intravasation into circulation, and homing into and extravasation towards the brain. The phenotypic change in malignant cells, and the importance of the microenvironment in the formation of brain metastases are also inspected. Finally, the importance of genetic and epigenetic changes, and the recently disclosed effects of microRNAs in brain metastasization of breast cancer are highlighted.

1. Breast cancer

Breast cancer (BC) is a malignant tumour that usually starts in the epithelial cells of the mammary ducts [1]. It is the most frequently diagnosed cancer in women, with estimated 1.7 million new cases worldwide and nearly 521,900 related deaths in 2012 [2]. The early detection of this cancer through a mammography screening increases the chances for successful treatment and consequently decreases the mortality from BC [3]. For early-stage BC, the typical treatment procedure involves either mastectomy (total removal of the breast) or lumpectomy (removal of breast tumour and some of the normal surrounding tissue) plus adjuvant treatment [4]. Early surgical intervention has made an impact in preventing the recurrence of BC. However, this solid cancer is not always timely diagnosed, and in more aggressive and advanced stages the recurrence at distant organs is overwhelming.

All cancers are classified at diagnosis due to its importance for prognosis and responsiveness to therapy. One of the most widely used BC classification distributes BC patients in three groups according to the expression of receptors in BC cells (BCCs): hormone receptor-positive when patient presents either oestrogen receptor or progesterone receptor; human epidermal growth factor receptor 2 (HER2)-positive when HER2 is overexpressed; and triple-negative when the patient is hormone receptors-negative and HER2-negative [5], which is the group with worse survival. So, understanding of each group of patients at a molecular level allows not only deciding the most effective treatment for each patient and developing more specific therapeutic drugs, but also to study the cell behaviour according to its receptor status. When the cancer reaches its most advanced or metastatic stage, tumour cells have the ability to spread and form new tumours in distant visceral organs, such as lungs, liver, and brain, and/or in non-visceral organs that include bone and skin [6]. The arrest and growth of malignant cells in 'target organs' present a preferential distribution and location, a process called organotropism [7]. The organotropism depends on the following factors: the receptor status of BCCs; the circulatory pattern, although the most frequently organs metastasized by BCCs do not have

Abbreviations: 12(S)-HETE, 12(S)-hydroxyeicosatetraenoic acid; ADAM, A disintegrin and metalloproteinase; AJ, adherens junction; BBB, blood-brain barrier; BC, breast cancer; BCC, breast cancer cell; BM, basement membrane; BMVEC, brain microvascular endothelial cell; CD, cluster of differentiation; CNS, central nervous system; CTC, circulating tumour cell; Cx, connexin; CXCL12, cysteine-X amino acid-cysteine ligand 12; CXCR4, cysteine-X amino acid-cysteine receptor 4; EC, endothelial cell; E-cadherin, epithelial cadherin; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial-mesenchymal transition; EndMT, endothelial-mesenchymal transition; E-selectin, endothelial selectin; GABA, γ-aminobutyric acid; GJ, gap junction; HER2, human epidermal growth factor receptor; HGFR, hepatocyte growth factor receptor; HGF/SF, hepatocyte growth factor/scatter factor; ICAM, intercellular adhesion molecule; JAM, junctional adhesion molecule; MET, mesenchymal-epithelial transition; miRNA, microRNA; MLC, myosin light chain; MLCK, myosin light chain kinase; MMP, matrix metalloproteinase; MUC1, mucin 1; N-cadherin, neuronal cadherin; PSGL-1, platelet selectin glycoprotein ligand-1; sLe^x, sialyl Lewis x; TEM, transendothelial migration; TGFβ, transforming growth factor beta; TJ, tight junction; VCAM-1, vascular cell adhesion molecule-1; VE, vascular endothelial; VEGF, vascular endothelial growth factor; ZO, zonula occludens

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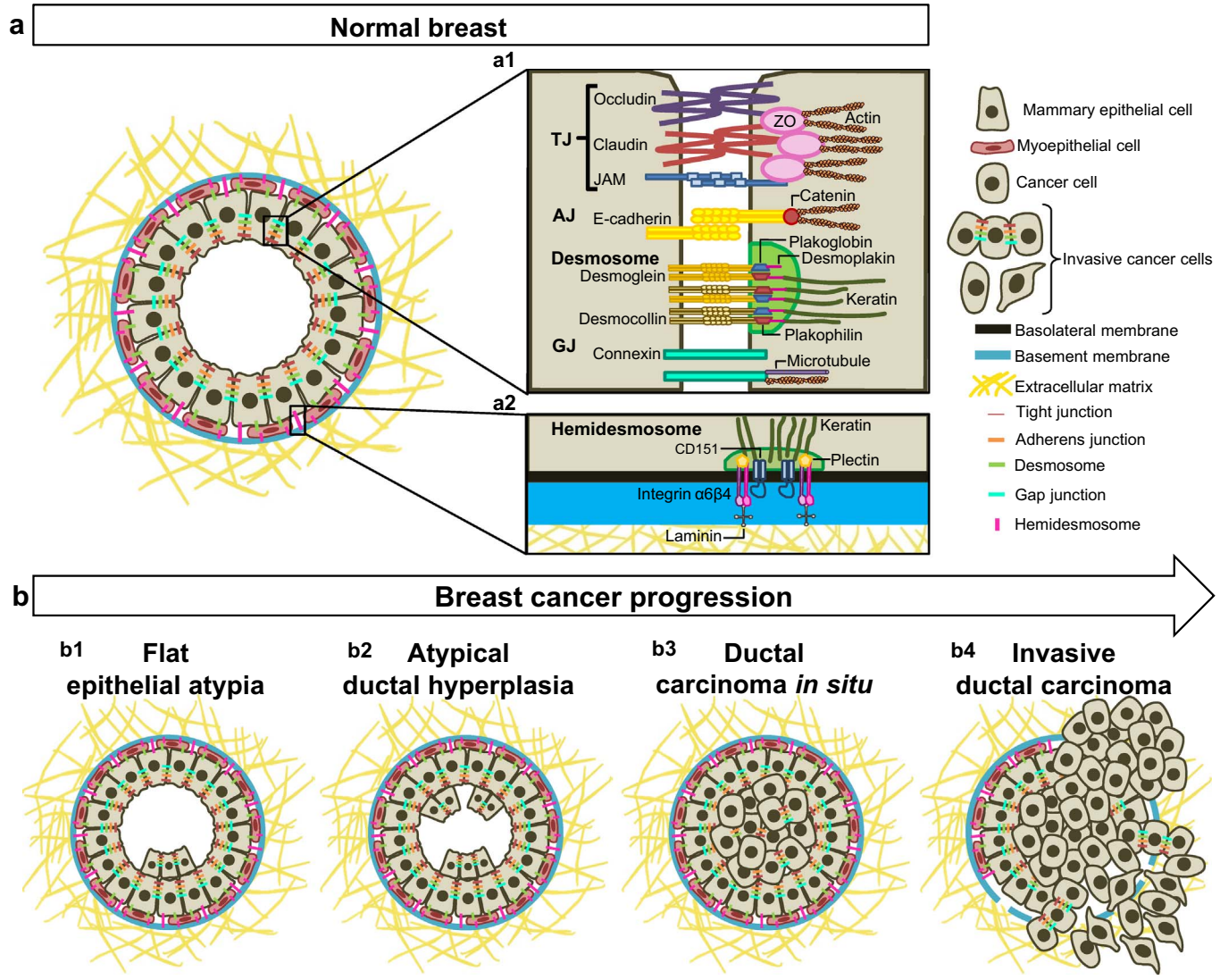

Fig. 1. Schematic representation of the mammary duct and of the alterations occurring during the progression of breast cancer. In normal breast, the mammary duct is lined by polarized epithelial cells that are surrounded by myoepithelial cells, encircled by a basement membrane (BM), and embedded in the extracellular matrix (ECM). Mammary epithelial cells establish interactions with neighbouring cells through intercellular junctions composed by tight junction (TJ), adherens junction (AJ), desmosome, and gap junction (GJ) and interactions with BM through hemidesmosomes (a). All junctions are formed by transmembrane and cytosolic proteins, which in turn provide attachment to cytoskeleton proteins. TJs include the transmembrane proteins occludin and proteins of the claudin and junction adhesion molecule (JAM) families and the cytosolic proteins of the zonula occludens (ZO) family, which bind to the cytoskeleton protein actin; AJs include the transmembrane endothelial-cadherin (E-cadherin) that is associated with cytosolic proteins of the catenin's family, responsible for the attachment to actin; desmosomes are formed by the transmembrane adhesion proteins desmoglein and desmocollin that belong to cadherin family and cytosolic desmosomal plaque proteins desmoplakin, plakoglobin and plakophilin that anchor the cytoskeleton keratinous intermediate filaments to the plasma membrane; GJs are composed by the transmembrane proteins connexins that establish interactions with the cytoskeleton, namely through microtubules and actin (a1). Hemidesmosomes are formed by transmembrane proteins integrin α6β4, and cluster of differentiation (CD)151 that act as cell receptors connecting the cell and the ECM, cytoplasmic plaque protein plectin responsible for the linkage of cytoskeleton to the cell surface, and the BM-associated proteins laminins that mediate the adhesion to the ECM. The development of breast primary tumour (b) occurs through a step-wise progression from benign flat epithelial atypia to atypical ductal hyperplasia (b1 and b2), two precursor lesions characterized by intraductal proliferation of epithelial cells resulting in multi-layering of ductal epithelium; it evolves into malignant ductal carcinoma *in situ* (b3), another intraductal proliferative lesion characterized by lacking ductal organization, but restricted to breast ducts; and finally to invasive ductal carcinoma (b4) that consists in an extensive growth of the malignant cells beyond the ductal structure and the BM.

an immediate direct vascular connection with the primary tissue; genetic signatures present in tumour cells that orchestrate and control the metastatic tropism; and the microenvironment of the organ that will be metastasized [8,9].

Central nervous system (CNS) metastases from BC occur in 15–25% of patients, representing the second most frequent cause of metastasization to the CNS, after lung cancer [10]. Brain metastasis is commonly associated with poor prognosis and diminished quality of life, being normally a catastrophic life-threat outcome for patients with solid cancers, such as BC [11]. In fact, the 1-year survival rate of patients with metastatic BC to the CNS was reported as only 20% [12]. Moreover, there are no targeted therapies specific for this secondary tumour formation, and it is expected that the incidence of brain metastases continues to increase [13,14]. To this increased incidence of brain metastases can contribute factors such as: the improvement of quality of life and survival of patients that received treatment for BC; the peculiar characteristics of the brain since the blood-brain barrier (BBB) prevents CNS penetration of most of the conventional and new chemotherapeutic agents and the glial cells of cerebral microenvironment render malignant cells resistant to therapy; and the increased use of refined imaging and the greater attention paid to neurological signs or symptoms [15–17]. Brain metastasization varies according to the receptor status of BCCs. In fact, both HER2-positive and triple-negative BC subtypes are the most associated with the development of CNS metastases, when compared with hormone receptor-positive patients, with incidences of brain metastasis achieving values as high as 30–40%