

# Basic ductal carcinoma in situ (DCIS) pathobiology for modelers

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## Abstract

Ductal carcinoma in situ (DCIS)—a significant precursor to invasive breast cancer—is typically diagnosed as microcalcifications in mammograms. In this brief tutorial (originally prepared for Macklin et al. (2012)), we provide essential background for modelers working in ductal carcinoma in situ of the breast. For more information on tumor biology for modelers, please visit [MathCancer.org](http://MathCancer.org), and refer to Macklin (2010).

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## 1 Introduction

Ductal carcinoma in situ (DCIS), a type of breast cancer where growth is confined within the breast ductal/lobular units, is the most prevalent precursor to invasive ductal carcinoma (IDC). Breast cancer is the second-leading cause of death in women in the United States. The American Cancer Society predicted that 50,000 new cases of DCIS alone (excluding other pre-invasive cancers such as lobular carcinoma in situ) and 180,000 new cases of IDC would be diagnosed in 2007 (Jemal et al., 2007; American Cancer Society, 2007). Co-existing DCIS is expected in 80% of IDC (Lampejo et al., 1994). While DCIS itself is not life-threatening, it is clinically important because it can be effectively treated and if left untreated,

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it has a high probability of progression to IDC (Page et al., 1982; Kerlikowske et al., 2003; Sanders et al., 2005). While the detection and treatment of DCIS have greatly improved over the last few decades, problems persist. DCIS can be difficult to detect by mammography (the principal modality in breast screening) or to distinguish from other aberrant lesions (Venkatesan et al., 2009). This can lead to “false positives” of DCIS and overtreatment, including unnecessary surgery. When excision is warranted, re-surgery is required in 20-50% of cases to fully eliminate all DCIS (Talsma et al., 2011), highlighting difficulties in estimating the full DCIS extent from patient imaging (Cheng et al., 1997; Silverstein, 1997; Cabioglu et al., 2007; Dillon et al., 2007). A solid scientific understanding of DCIS progression is required to improve surgical and therapeutic planning.

## 2 Biology of breast duct epithelium

The breast is organised as a system of 12-15 independent, largely parallel duct systems: clusters of milk-producing lobules (collectively referred to as TDLUs: terminal ductal lobular units) that feed into a branched duct system that terminates at the nipple (Wellings et al., 1975; Moffat and Going, 1996; Ohtake et al., 2001; Going and Mohun, 2006). See Fig. 1. The duct systems are separated by supporting ligaments and fatty tissue and drained by the lymphatic system (Tannis et al., 2001). Each duct is a tubular arrangement of epithelial cells that enclose a fluid-filled lumen. The epithelium, in turn, is surrounded by myoepithelial cells (epithelial cells with contractile properties to transport milk) and a basement membrane (BM). Surrounding the duct is the stroma, which is comprised primarily of a supporting scaffolding of fibers (the extracellular matrix, or ECM) and mesenchymal cells that maintain the ECM. The stroma is interlaced by blood vessels that supply oxygen and other vital substrates to the tissue. See Fig. 2 (top left). Note that the breast epithelium has no direct access to oxygen and nutrients; these must diffuse into the duct through the BM.

The epithelial cells are *polarized*: integrins on a well-defined basal side adhere to the basement membrane, E-cadherin molecules on the lateral sides adhere to neighboring cells, and the apical side has relatively few adhesion molecules. See Fig. 2 (top right). The epithelial cell arrangement in the duct depends critically upon this polarization and the resulting nonuniform distribution of adhesive forces (Jiang and Chuong, 1992; Hansen and Bissell, 2000; Wei et al., 2007; Butler et al., 2008).

While the epithelial cell population oscillates with the menstrual cycle (Khan et al., 1998, 1999), on average proliferation and apoptosis balance to maintain homeostasis. Microenvironmental changes can trigger signaling responses that lead to proliferation or apoptosis, which ordinarily helps to safeguard the normal tissue architecture. For example, a decrease of E-cadherin signaling (following apoptosis in a neighboring cell) can increase  $\beta$ -catenin signaling, which eventually increases proliferation to replace the missing cell (Conacci-Sorrell et al., 2002; Hansen and Bissell, 2000; Wei et al., 2007). Adhesion to the BM triggers integrin signaling and downstream production of survival proteins that inhibit apoptosis (Ilić et al., 1998; Giancotti and Ruoslahti, 1999; Stupack and Chersesh, 2002). Loss of attachment to the BM therefore allows one type of apoptosis (*anoikis*) to occur, thus preventing overgrowth

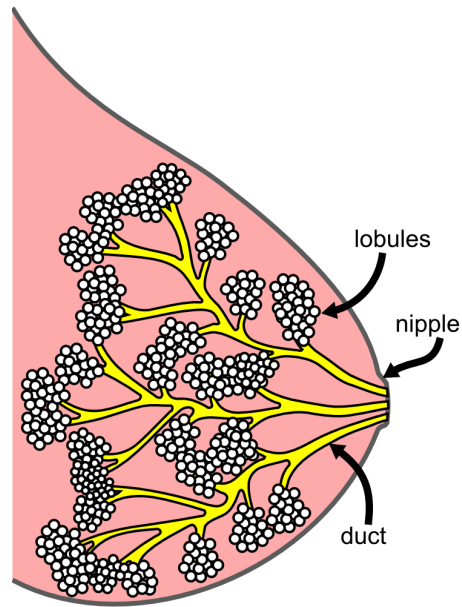


Figure 1: Basic architecture of the breast lobular-ductal system. An advance copy of this figure appeared in Macklin et al. (2009, 2010a).

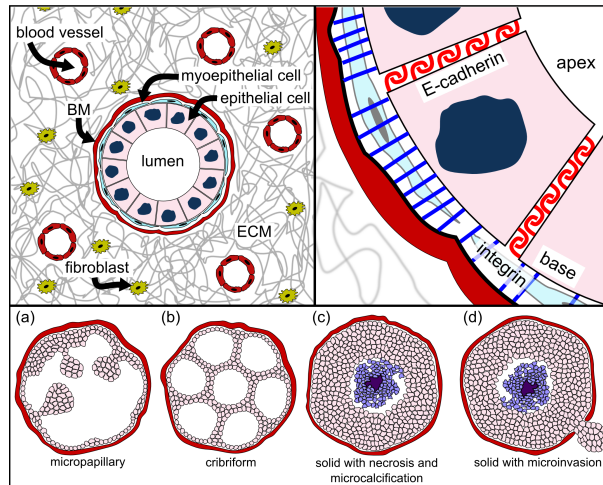


Figure 2: *Top Left*: Typical breast duct microanatomy. *Top Right*: Breast duct epithelial cell polarization. *Bottom*: Major DCIS types and invasive ductal carcinoma. An advance copy of this figure appeared in Macklin et al. (2009, 2010a).

of cells into the lumen (Danes et al., 2008). Hormones such as estrogen, progesterone, prolactin, and epidermal growth factor can affect epithelial cell proliferation and apoptosis prior to lactation (Anderson, 2004), during breast involution (Baxter et al., 2007), and in cancer (Simpson et al., 2005).

### 3 Biology of DCIS

Overexpressed oncogenes and underexpressed tumor suppressor genes can disrupt the balance of epithelial cell proliferation and apoptosis, leading to overproliferation. This can occur typically either by the accumulation of DNA mutations (genetic damage) or DNA amplification (Simpson et al., 2005), or epigenetic anomalies (Ai et al., 2006). The transformation from regular breast epithelium to carcinoma is thought to occur in stages. For simplicity, we set aside the relatively benign precursor transformations (e.g., atypical ductal hyperplasia) which have a low risk for subsequent invasive breast cancer (Page, 1992) and focus on DCIS.

In the most well-differentiated classes of DCIS, the epithelial cells maintain their polarity and anisotropic adhesion receptor distributions, resulting in partial recapitulation of the non-pathological duct structure within the lumen. These demonstrate either finger-like growths into the lumen (micropapillary: see Fig. 2 (bottom:a)), or arrangements of duct-like structures (cribriform: see Fig. 2 (bottom:b)) (Silverstein, 2000). The cells in solid type DCIS lack polarity and do not develop these microstructures. Instead, the cells proliferate until filling the entire lumen (Fig. 2 (bottom:c)) (Danes et al., 2008). The proliferating cells uptake oxygen and substrates as they diffuse into the duct, causing substrate gradients to form. If the central oxygen level is sufficiently depleted, a necrotic core of debris forms (comedo-type solid DCIS: see Fig. 2 (bottom:c)) (Silverstein, 2000). These necrotic cells are typically not phagocytosed; instead, they swell and burst (Barros et al., 2001), and their solid (i.e., non-water) components are slowly calcified (Stomper and Margolin, 1994). It is these calcifications that are generally detected by mammograms when diagnosing DCIS (Ciatto et al., 1994). The BM blocks DCIS from invading the stroma, thereby impeding spread through the stroma, invasion into lymphovascular channels and hence metastasis. Further mutations can transform DCIS into invasive ductal carcinoma, whose cells move along the duct, secrete matrix metalloproteinases (MMPs) to degrade the BM, and subsequently invade the stroma (Fig. 2 (bottom:d)). See Silver and Tavassoli (1998) and Adamovich and Simmons (2003).

While it is tempting to regard DCIS as a linear progression from regular epithelium to cribriform or micropapillary (“partially transformed”) to solid type (“fully transformed”), the morphological and molecular pathway is currently an open question (Erbas et al., 2006; Rennstam and Hedenfalk, 2006). The excellent modeling and analysis by Sontag and Axelrod (2005) strongly refutes a linear progression model. On the other hand, recent modeling by Norton et al. (2010) hypothesized that cribriform DCIS progresses to solid-type DCIS when proliferation-induced pressures collapse the “microlumens” (the small lumens in the cribriform structure). The dominant type of DCIS in any particular case may depend upon the underlying molecular changes. For example, cribriform DCIS could arise from hyperproliferative cells where genes regulating polarization are functionally intact.

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