

# Histology of Normal Breast

## TERMINOLOGY

### Abbreviations

- Terminal ductal lobular unit (TDLU)

## INTRODUCTION

### Breast Origin and Function

- Breast is highly evolved modified skin appendage
  - Defining feature of class Mammalia
- Many important differences in comparison to other organs
  - Provides source of nourishment and immunologic protection for different individual (infant)
  - Undergoes continuous change over life cycle in response to menarche, pregnancy, lactation, and menopause
    - Target organ for variety of hormones that regulate development and physiologic function
    - Result in broad range of what is normal breast histology
  - Due to superficial location, breast has social, sexual, and cultural significance
    - Patients are 1st to diagnose their carcinomas in populations without screening
      - Breast cancer is only cancer with > 3,000 year history of 1st person accounts by patients

### Normal Breast (Rule of Twos)

- Breast has 2 types of epithelial cells, 2 types of stroma, and 2 main structures
  - Epithelial cell types
    - Luminal cells
    - Myoepithelial cells
  - Stroma
    - Interlobular stroma
    - Intralobular stroma
  - Structures
    - Large ducts
    - TDLU

## GROSS ANATOMY

### Anatomic Boundaries

- Breasts rest on anterior chest wall overlying pectoralis major and minor muscles
  - Superior border ~ at 2nd rib; inferior border at 6th rib; lateral border at mid axillary line; medial border at edge of sternum
  - Deep margin of breast rests on fascia of pectoralis major muscle
  - Breast tissue often extends into axilla (tail of Spence)
- In some women, breast tissue is present in subcutaneous tissue and can extend beyond grossly evident breast borders

### Suspensory (Cooper) Ligaments

- Ligaments attach to fascia of skin and pectoralis muscle
- Provide support and allow for mobility
- Swelling and edema of breast tissue around these ligaments causes orange peel appearance of skin (peau d'orange)
- Carcinoma involving these ligaments results in skin retraction &/or dimpling

### Nipple

- Positioned slightly medial and inferior to center of breast
- 10-15 major lactiferous duct orifices open on surface of nipple
  - Arranged radially in nipple
- Nipple-areolar complex supported by subdermal layer of circumferential smooth muscle
  - Facilitates nipple erection, function during nursing

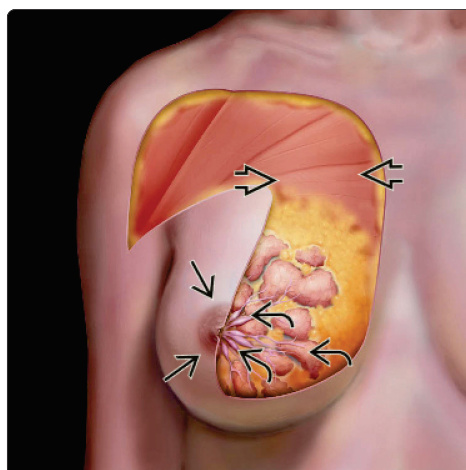
## MICROSCOPIC ANATOMY

### Nipple

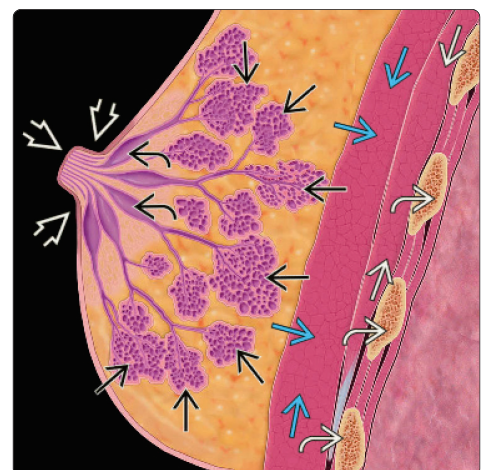
- Covered by pigmented squamous epithelium
  - Toker cells are normal epidermal component
    - Present in majority of nipples if identified by cytokeratin 7 studies
    - Usually present as single cells near nipple orifices

Adult Female Breast

(Left) The adult female breast is located on the anterior chest wall, overlying the pectoralis muscles. The nipple-areolar complex is located slightly inferior to center. 15-20 major ductal systems empty onto the skin at the nipple. (Right) The major breast structures are the nipple-areolar complex, the large duct system, and the terminal duct lobular units. The pectoralis major muscle and the pectoralis minor overlie the ribs of the chest wall connected by intercostal muscles.



Breast Structure



- Appearance and immunoprofile are same as luminal cells
  - Bland cells with clear or pale cytoplasm
  - Usually positive for hormone receptors
- Clear cells of nipple epidermis are keratinocytes with prominent glycogenated cytoplasm
  - Cells can mimic cells of Paget disease
- Ducts dilate to form lactiferous (milk) sinuses beneath nipple
  - Sinuses have serrated contours and are supported by smooth muscle, collagen, and elastic fibers
- Basement membrane of ducts is continuous with basement membrane of skin
  - Basement membrane surrounds entire mammary ductal/lobular system; separates epithelial cells from breast stroma
    - Consists of type IV collagen and laminin
  - Elastic fibers normally present in varying amounts around mammary ducts but not lobules
  - With age, supporting structures of major ducts can weaken, allowing extravasation of contents
- Keratin-producing squamous cells of epidermis extend into major ducts for 1-2 mm
  - Outside of lactation, keratin plug may be present in nipple orifice
  - Abrupt transition from squamous cells to normal luminal/myoepithelial lining of ducts

## Areola

- Lacks pilosebaceous units and hair except at periphery
- Numerous sensory nerve endings are present

## Skin Appendages

- Montgomery tubercles
  - Numerous sebaceous glands are present in areola
  - Open through small prominences at periphery of areola
  - Become more prominent during pregnancy and lactation
- Eccrine sweat glands and ducts
  - Present in breast dermis and skin
  - At other sites, syringomas arise from these glands
  - In breast, syringomatous adenomas of nipple are more closely related to breast epithelial cells
- Apocrine sweat glands and ducts
  - Present in axillary skin and areola
  - Apocrine metaplasia has same appearance of cells in sweat glands
    - Characterized by apocrine secretion due to presence of apocrine snouts that are pinched off to form secretions (decapitation secretion)
  - Nuclei are large and round with large single nucleoli
  - Cytoplasm is abundant, eosinophilic, and often has cytoplasmic granules

## Large Duct System

- 15-20 major duct systems empty at nipple
  - Additional smaller ductal systems open onto areola
- Ducts ramify until they form TDLUs
- Ductal systems vary considerably in size and extent, often overlap
  - Rarely confined to single quadrant
  - Size and extent vary greatly in different individuals

- Some large ducts branch and fill widely separate areas of breast
  - Cannot be recognized grossly; requires duct injection or serial section reconstruction
- Anastomoses between ductal systems may be present

## ● Significance for breast carcinoma

- DCIS is clonal population; involves single duct system
- Distribution of DCIS generally follows ductal system
- Multiple duct systems could be involved in following situations
  - DCIS grows into 2nd duct system by crossing into another duct orifice at nipple
  - DCIS crosses into 2nd duct system via 1 of reported anastomoses between ducts
  - 2 separate clonal neoplastic populations of DCIS are present

## Lobules

- Formed when terminal duct branches into multiple rounded acini (TDLU)
  - Functional unit of breast for milk production
- Lobulocentric architecture (duct surrounded by multiple acini)
  - Important in distinguishing benign lesions that maintain this architecture from malignant lesions that do not
- TDLU can unfold with coalescence of acini to form structures resembling ducts
- 50% of all glandular tissue located in upper outer quadrant
- Majority of breast lesions arise from the TDLU
  - Cysts, epithelial hyperplasia, sclerosing adenosis, and majority of carcinomas are thought to arise from TDLU

## EPITHELIAL CELLS

### Epithelial Cell Types

- 2 types of epithelial cells are present in breast: Luminal cells and myoepithelial cells
  - Precursor/progenitor or stem cells may be present; special techniques are required for recognition
    - Sometimes referred to as intermediate or basal cells
    - May give rise to both luminal and myoepithelial cells
      - Supported by occurrence of clonal neoplasms composed of both cell types (e.g., myoepitheliomas, adenoid cystic carcinoma)
  - Patchy immunoreactivity for high molecular weight cytokeratins 5/6 in epithelial hyperplasia supports presence of mixed population of multiple cells types

### Luminal Cells

- Form innermost layer lining ducts and acini
  - Luminal cells in TDLU produce milk
  - Luminal cells in larger ducts do not undergo lactational change or produce milk
- Cells are cuboidal to columnar in shape
  - Nuclei are small, round to oval, usually have inconspicuous nucleoli
  - Cells have moderate amount of eosinophilic cytoplasm
- Luminal cell phenotype
  - Usually express luminal low molecular weight keratins 7, 8, 18, 19
    - May also express basal keratins

# Histology of Normal Breast

- Some but not all luminal cells express ERα &/or PR at any given time
  - Hormone receptors are not expressed in normal proliferating luminal cells
  - Receptor (+) cells are present in both large duct system and TDLU but may be more frequent in latter
- Cells express E-cadherin and other catenins
- Some luminal cells express mammaglobin &/or gross cystic disease fluid protein 15 (GCDFP-15)
- Luminal cells are thought to be precursor cells for majority of breast carcinomas

## Myoepithelial Cells

- Form outermost layer between luminal cells and basement membrane
- Cells form contractile meshwork that does not cover entire basement membrane
  - In cross section, myoepithelial cells (MEC) layer is incomplete
- Multiple functions
  - Help produce and maintain basement membrane
    - Lesions of myoepithelial cells often associated with matrix production
  - Aid in luminal cell polarity
  - Inhibit angiogenesis
  - Contract for milk ejection during breast feeding
- Often flattened with small, round nuclei
  - Cytoplasm can be abundant and clear; may mimic lobular neoplasia
  - With aging, cells can become prominent and spindled in shape (MEC atrophy)
- **Myoepithelial cell phenotype**
  - Usually express high molecular weight basal keratins 5/6, 14, 17
    - May also express luminal keratins
  - Express contractile proteins: Smooth muscle actin, calponin, smooth muscle myosin heavy chain
  - Also express p63, CD10, P-cadherin, S100, mappsin
  - Do not express hormone receptors
  - MEC associated with carcinoma in situ may diminish in number and become displaced from basement membrane
    - Often fail to express some MEC markers
  - Complete loss of MEC is useful diagnostic feature to help recognize invasive carcinoma
  - May be precursors of some hormone receptor negative carcinomas
    - Basal used to describe carcinomas that may arise from MEC or MEC-like cell
    - Many of these carcinomas express proteins found in MECs

## Metaplastic Changes

- Epithelial cells can take on different appearances due to injury, hormonal influences, or other unknown factors
- Cells look monomorphic due to metaplasia
  - It can be very difficult to distinguish some cases of metaplasia from carcinomas with metaplastic appearance
- **Squamous metaplasia**

- Breast epithelial cells can take on squamous phenotype in response to injury or inflammation
- Different appearance can often raise concern for atypia or neoplasia
- Rare squamous carcinomas arise from areas of squamous metaplasia in cysts
  - Presence of spindled population of epithelial cells in stroma is generally diagnostic of carcinoma
- **Apocrine metaplasia**
  - Very common change in cells lining cystic spaces and in papillomas
    - Resemble apocrine sweat glands
    - Apocrine cells often express androgen receptor and show immunoreactivity for HER2
  - Mixed apocrine and nonapocrine populations favor benign lesion
  - Nuclei are large and round with prominent single nucleoli
  - Cytoplasm is abundant and eosinophilic
    - Red cytoplasmic granules often present
    - Apocrine snouts common
- **Clear cell change**
  - Cytoplasm is abundant and clear
  - Nuclei often small, hyperchromatic, and round
  - Can be present in either luminal cells or myoepithelial cells
- **Columnar cell change**
  - Luminal cells have a tall columnar shape rather than being cuboidal
  - If more than 1 cell layer is present, termed columnar cell hyperplasia
- **Paneth cell-like change**
  - Luminal cells have brightly eosinophilic cytoplasmic granules
    - May be related to apocrine metaplasia
  - Associated with eosinophilic colloid-like secretions
  - Can be associated with microglandular adenosis and rare carcinomas

## MAMMARY STROMA

### Composition

- Breast stromal composition depends on age, menstrual status, pregnancy history, and lactation
  - Composed of varying amount of fibrous connective and adipose tissue
  - Ratio of ductal/fibrous tissue to adipose tissue varies between individuals and changes over time
    - Important determinant of mammographic density
  - Mammographic appearance
    - In young women, breast tissue is predominantly fibrous (radiodense or white)
      - Mammography has low sensitivity due to difficulty detecting lesions
    - With age, fibrous stroma is replaced by adipose tissue
    - In older women, breast may be predominantly adipose tissue (radiolucent or black)
      - Mammography has greater sensitivity as calcifications and small masses are detected more easily

# Histology of Normal Breast

Anatomic Structures and Associated Lesions			
Anatomic Structure	Function	Inflammatory Lesions	Hyperplasia/Tumor
Nipple/areola	Milk ejection	Squamous metaplasia of lactiferous ducts (SMOLD)	Nipple adenoma, leiomyoma, syringomatous adenoma, Paget disease
Large duct system	Conduit for milk	Duct ectasia	Papilloma, encapsulated papillary carcinoma,
Terminal ductal lobular unit (TDLU)	Luminal cells: Milk production; myoepithelial cells: Contraction for milk ejection	Cysts (rupture), granulomatous lobular mastitis, lymphocytic mastopathy	Epithelial hyperplasia, sclerosing adenosis, carcinomas
Interlobular stroma	Size, shape, motility of breast	Fat necrosis, bacterial infection	Lipoma, angioliipoma, hemangioma, fibromatosis, nodular fasciitis, fibrous tumors, myofibroblastoma, pseudoangiomatous stromal hyperplasia, sarcoma
Intralobular stroma	Function and support of TDLU	Granulomatous lobular mastitis, lymphocytic mastopathy	Fibroadenoma, phyllodes tumor

Cell Types of Breast			
Cell Types	Function	Protein Expression	Lesions
Luminal cells	TDLU: Milk production; Ducts: Conduit for milk	Luminal keratins 7, 8, 18, E-cadherin, estrogen and progesterone receptor	Epithelial hyperplasia, atypical hyperplasia, majority of carcinomas
Myoepithelial cells	Support basement membrane, maintenance of luminal cell polarity, contraction for milk ejection	Basal keratins 5/6, 14, 17, P-cadherin, muscle markers, p63, CD10, podoplanin (D2-40)	Myoepitheliomas, collagenous spherulosis, possible subset of triple- negative carcinomas
Stromal fibroblasts and myofibroblasts	Support of epithelial cells, provide majority of breast volume	CD34 (majority), muscle markers (myofibroblasts), estrogen and progesterone receptors (myofibroblasts)	Pseudoangiomatous stromal hyperplasia (PASH), fibrous tumors, desmoid fibromatosis, myofibroblastoma, fibroadenoma/phyllodes tumors

□ Obesity and postmenopausal hormone use can act to maintain breast tissue density

### • Interlobular stroma

- Responsible for majority of breast volume
- Increase in breast size at puberty is primarily due to increase in interlobular stroma
  - Hormonal influences on this stroma are poorly understood
- Cellular components of stroma include fibroblasts, myofibroblasts, adipocytes, blood and lymphatic vessels
  - Majority of fibroblasts and myofibroblasts CD34(+)
  - Some myofibroblasts are ER &/or PR(+)
  - Large, hyperchromatic, multinucleated stromal cells can be seen and may be due to degenerative changes
- Variety of lesions that can occur in and outside of breast arise from this stroma
  - Breast and other sites: Lipoma, angioliipoma, hemangioma, nodular fasciitis, fibromatosis
  - Most common in breast: Myofibroblastoma and angiosarcoma
  - Only breast: Pseudoangiomatous stromal hyperplasia (PASH)

### Intralobular Stroma

- Surrounds and supports acini of TDLU

- Looser more cellular appearance compared with interlobular stroma
- Often has scattered lymphocytes and plasma cells
  - May be myxoid in appearance
- Lesions of this stroma are specific to breast and are biphasic
  - Hyperplasias are due to increased growth of both stroma and epithelium
  - Neoplasias are due to proliferation of clonal stromal population that stimulates growth of nonclonal epithelium
    - Fibroadenomas and phyllodes tumors

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