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The role of cytokeratin 5 in breast lobular myoepithelial cells

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Abstract
Cytokeratin 5 (CK5) is a type II intermediate filament protein predominantly expressed in the basal epithelial cells of various tissues, including the breast. In breast tissue, CK5 plays a crucial role in maintaining the structural integrity and function of myoepithelial cells, which are essential for proper breast development and homeostasis. This review aims to provide a comprehensive analysis of CK5's role in breast lobular myoepithelial cells, focusing on its expression patterns, regulatory mechanisms, and potential implications in breast cancer pathogenesis. By exploring the current literature, this review will highlight the importance of CK5 as both a marker for myoepithelial cells and a potential diagnostic and prognostic tool in breast cancer, particularly in lobular carcinoma. Additionally, the review will discuss the potential of CK5 as a therapeutic target, considering its involvement in epithelial-mesenchymal transition (EMT) and tumor invasion.

Keywords: EMT, NAFLD, tumor invasion, cytokeratin, myoepithelial cells, expression patterns, regulatory mechanisms

Introduction
Breast tissue comprises a complex architecture of epithelial and myoepithelial cells that form the ductal and lobular units. Myoepithelial cells, located between the luminal epithelial cells and the basement membrane, play a pivotal role in maintaining the structural and functional integrity of the breast. Cytokeratin 5 (CK5) is one of the key cytoskeletal proteins expressed in myoepithelial cells, contributing to their contractile function and providing a marker for identifying these cells in both normal and pathological conditions.
This review delves into the specific role of CK5 in breast lobular myoepithelial cells, examining its expression patterns under normal physiological conditions and in the context of breast cancer. Given the growing interest in CK5 as a biomarker and therapeutic target, this review synthesizes the current understanding of CK5's biological functions and its potential clinical applications.

Objective of the paper
The main objective of this paper is to comprehensively examine the role of Cytokeratin 5 (CK5) in breast lobular myoepithelial cells, focusing on its expression, function, and implications in breast cancer pathogenesis, with the aim of exploring its potential as a diagnostic marker and therapeutic target.

Cytokeratin 5: Structure and Function
Cytokeratin 5 (CK5) is a fundamental component of the cytoskeleton in epithelial cells, particularly within the basal layer of various tissues, including the breast. As a type II intermediate filament, CK5 forms heterodimers with type I keratins, such as CK14, contributing to the structural stability and mechanical resilience of epithelial cells. The cytoskeletal network formed by CK5 plays a critical role in maintaining the integrity of the epithelial cell layer, facilitating essential cellular processes such as shape maintenance, signal transduction, and intracellular transport.
CK5 is highly expressed in the basal cells of stratified epithelia, where it provides a structural framework that resists mechanical stress. This property is particularly important in tissues that undergo constant physical stress, such as the skin and the mammary gland.

In the mammary gland, CK5 expression is predominantly observed in myoepithelial cells, which lie between the luminal epithelial cells and the basement membrane. These myoepithelial cells are contractile in nature, contributing to the ejection of milk during lactation by facilitating the contraction of alveoli in response to oxytocin.

The functional role of CK5 extends beyond mere structural support. CK5 is involved in the regulation of various cellular processes, including cell polarity, differentiation, and adhesion. Studies have shown that CK5, along with its partner CK14, is critical in maintaining the basal epithelial phenotype. The presence of CK5 is often indicative of the basal-like phenotype, which is associated with a specific subset of breast cancers known for their aggressive behavior. The expression of CK5 is regulated by several signaling pathways, including the Notch and p63 pathways. These pathways are crucial for the differentiation and maintenance of basal epithelial cells, and dysregulation in these pathways can lead to aberrant CK5 expression, contributing to pathological conditions, including cancer.

Recent studies have also highlighted the role of CK5 in the epithelial-mesenchymal transition (EMT), a process where epithelial cells lose their characteristic features and gain mesenchymal properties, such as increased motility and invasiveness. CK5 has been implicated in maintaining the epithelial phenotype, and its down regulation is often associated with the initiation of EMT. This function positions CK5 as a critical player in the suppression of tumor progression and metastasis, emphasizing its importance in the context of cancer biology.

CK5 Expression in Breast Lobular Myoepithelial Cells

In breast tissue, CK5 expression is predominantly localized to the myoepithelial cells, which are essential for maintaining the structural and functional integrity of the mammary gland. These cells form a continuous layer around the epithelial cells of the ducts and lobules, contributing to the maintenance of the basement membrane and preventing the invasion of luminal cells into the surrounding stroma. The expression of CK5 in these cells is a marker of their basal phenotype, and it plays a critical role in their contractile function, which is essential for the ejection of milk during lactation. CK5 expression in breast lobular myoepithelial cells is regulated by a combination of transcription factors and signaling pathways, including p63 and Notch signaling. These pathways are crucial for the differentiation and maintenance of the basal myoepithelial phenotype. Aberrations in these pathways can lead to alterations in CK5 expression, which can have significant implications for breast tissue homeostasis and the development of breast cancer. Studies have shown that CK5 expression in myoepithelial cells can be altered in the context of breast cancer. In particular, a reduction or complete loss of CK5 expression has been observed in myoepithelial cells surrounding malignant lesions, particularly in invasive lobular carcinoma (ILC). This loss of CK5 expression is associated with a loss of the contractile function of myoepithelial cells, which can lead to a breakdown of the basement membrane and facilitate the invasion of cancer cells into the surrounding stroma. The alteration in CK5 expression in myoepithelial cells is also associated with changes in their interaction with the extracellular matrix. CK5 is involved in the regulation of cell-matrix interactions, and its loss can lead to alterations in the expression of matrix metalloproteinases (MMPs), which are enzymes that degrade the extracellular matrix and facilitate tumor invasion. The loss of CK5 expression in myoepithelial cells may also lead to a loss of their tumor-suppressive properties, contributing to the progression of breast cancer.

CK5 and Breast Cancer Pathogenesis

The role of CK5 in breast cancer pathogenesis is multifaceted, involving its function in maintaining the basal epithelial phenotype, regulating cell adhesion, and suppressing epithelial-mesenchymal transition (EMT). In breast cancer, particularly in invasive lobular carcinoma (ILC), the loss of CK5 expression in myoepithelial cells is associated with a breakdown of the epithelial-myoepithelial barrier, facilitating the invasion of cancer cells into the surrounding stroma. One of the key roles of CK5 in breast cancer pathogenesis is its involvement in maintaining the integrity of the myoepithelial cell layer. Myoepithelial cells play a critical role in maintaining the basement membrane and preventing the invasion of luminal epithelial cells into the surrounding stroma. The loss of CK5 expression in myoepithelial cells can lead to a breakdown of this barrier, allowing cancer cells to invade the surrounding tissue and metastasize to distant sites. CK5 is also involved in regulating cell adhesion and polarity, which are critical for maintaining the structural integrity of epithelial tissues. In breast cancer, the loss of CK5 expression is associated with a loss of cell adhesion and polarity, which can contribute to the initiation of epithelial-mesenchymal transition (EMT). EMT is a process where epithelial cells lose their characteristic features and gain mesenchymal properties, such as increased motility and invasiveness. The initiation of EMT is a key step in the progression of cancer, as it allows cancer cells to invade surrounding tissues and metastasize to distant sites. Studies have shown that CK5 is a critical player in the suppression of EMT. CK5 expression is associated with the maintenance of the epithelial phenotype, and its down regulation is often observed in cancer cells undergoing EMT. The loss of CK5 expression in myoepithelial cells may contribute to the initiation of EMT in breast cancer, facilitating tumor progression and metastasis. In addition to its role in EMT, CK5 is also involved in regulating the expression of matrix metalloproteinases (MMPs), which are enzymes that degrade the extracellular matrix and facilitate tumor invasion. The loss of CK5 expression in myoepithelial cells is associated with increased expression of MMPs, contributing to the breakdown of the basement membrane and facilitating tumor invasion.

Diagnostic and Prognostic Implications

CK5 has emerged as a valuable diagnostic and prognostic marker in breast cancer. The expression of CK5 is often used to identify basal-like breast cancers, which are a subset of breast cancers that are characterized by their aggressive behavior and poor prognosis. Basal-like breast cancers typically express CK5, along with other basal markers such as CK14 and p63, and are often triple-negative, meaning they lack expression of estrogen receptor (ER), progesterone receptor (PR), and HER2/neu.

The expression of CK5 in myoepithelial cells is also used as a diagnostic marker to differentiate between benign and malignant breast lesions. In benign lesions, myoepithelial

cells typically express CK5, which can be detected by immunohistochemical staining. In contrast, the loss of CK5 expression in myoepithelial cells is often observed in malignant lesions, particularly in invasive lobular carcinoma (ILC). The presence or absence of CK5 expression in myoepithelial cells can provide valuable diagnostic information and help distinguish between benign and malignant lesions.

CK5 expression is also associated with patient outcomes in breast cancer. Studies have shown that CK5-positive tumors are often associated with a more aggressive clinical course and poorer prognosis. The expression of CK5 in breast cancer cells has been linked to increased tumor invasiveness and a higher likelihood of metastasis. As such, CK5 expression levels could potentially be used to stratify patients for tailored therapeutic approaches, with CK5-positive tumors being treated more aggressively.

In addition to its role as a diagnostic and prognostic marker, CK5 is also being investigated as a potential therapeutic target in breast cancer. Given its involvement in maintaining the epithelial phenotype and suppressing EMT, targeting CK5 could potentially prevent tumor progression and metastasis. Therapeutic strategies aimed at restoring CK5 expression in myoepithelial cells could reinforce the epithelial-myoepithelial barrier and limit tumor invasion.

CK5 as a Therapeutic Target

The potential of CK5 as a therapeutic target in breast cancer is gaining increasing attention, particularly in the context of its role in suppressing epithelial-mesenchymal transition (EMT) and maintaining the integrity of the epithelial-myoepithelial barrier. CK5 is involved in regulating various cellular processes that are critical for maintaining the epithelial phenotype, and its loss is associated with tumor progression and metastasis.

One potential therapeutic strategy is to restore CK5 expression in myoepithelial cells. Restoring CK5 expression could reinforce the epithelial-myoepithelial barrier, preventing the invasion of cancer cells into the surrounding stroma and limiting tumor progression. This could be achieved through gene therapy approaches that deliver functional copies of the CK5 gene to myoepithelial cells, or through the use of small molecules that upregulate CK5 expression.

Conclusion

Cytokeratin 5 (CK5) plays a pivotal role in the structure and function of breast lobular myoepithelial cells, with significant implications for breast tissue homeostasis and the pathogenesis of breast cancer. As a critical component of the cytoskeleton, CK5 is integral to maintaining the structural integrity of myoepithelial cells, contributing to their contractile function and ensuring the stability of the epithelial-myoepithelial barrier. The dysregulation of CK5 expression in these cells is closely associated with the progression of breast cancer, particularly invasive lobular carcinoma (ILC), where a loss of CK5 is linked to the breakdown of tissue architecture and the facilitation of tumor invasion.

CK5's role extends beyond its structural functions, encompassing its involvement in cellular processes such as adhesion, polarity, and epithelial-mesenchymal transition (EMT). The loss of CK5 expression not only weakens the protective barrier of myoepithelial cells but also promotes EMT, a key driver of cancer metastasis. These multifaceted roles underscore the importance of CK5 as both a marker and a mediator of breast cancer pathogenesis.

From a clinical perspective, CK5 has emerged as a valuable diagnostic and prognostic marker. Its expression patterns in breast tissue provide critical insights into the nature of breast lesions, helping to distinguish between benign and malignant conditions. Moreover, CK5 expression levels can inform treatment decisions, offering a potential stratification tool for identifying patients who may benefit from more aggressive therapeutic interventions.

The potential of CK5 as a therapeutic target is a promising avenue for future research. Strategies aimed at restoring or modulating CK5 expression could offer new approaches to preventing tumor progression and metastasis, particularly in CK5-negative breast cancers. By reinforcing the epithelial-myoepithelial barrier and inhibiting EMT, such therapies could enhance the effectiveness of existing treatments and improve patient outcomes.

In conclusion, CK5 represents a critical component of breast lobular myoepithelial cell biology with profound implications for breast cancer research and treatment. Continued investigation into the mechanisms regulating CK5 expression and function, as well as the development of targeted therapies, will be essential for advancing our understanding of breast cancer and improving therapeutic strategies. As research progresses, CK5 may well become a cornerstone in the fight against breast cancer, offering new hope for patients facing this challenging disease.

Conflict of Interest

The authors certify that they have no involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this paper.

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