DOG1/ANO1 in Breast Pathology: Diagnostic Utility, Interpretive Pitfalls, and Biological Significance

Sagda Mohamed Morgan[1]; Yousria Mohamed El-Gohary[1]; Hanaa A. Atwa [1]; Basma Hamed Ibrahim[1]
[1]Department of Pathology, Faculty of Medicine, Zagazig University, Zagazig, Egypt

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Abstract

Background: Demonstration of the myoepithelial cell layer is central to separating benign and in-situ breast proliferations from invasive carcinoma. Conventional markers are valuable but imperfect because staining may be attenuated in ductal carcinoma in situ, duplicated by tumor cells, or obscured by stromal and vascular cross-reactivity. DOG1, the immunohistochemical surrogate of the calcium-activated chloride channel ANO1/TMEM16A, has emerged as a complementary breast myoepithelial marker.

Aim: To review the biological basis, staining characteristics, diagnostic evidence, practical applications, and limitations of DOG1 in breast pathology.

Review content: DOG1 usually produces membranous and cytoplasmic staining in myoepithelial cells around normal ducts, lobules, many benign proliferations, and most in-situ carcinomas, with little stromal or vascular staining. Published series demonstrate substantial agreement with p63, calponin, and smooth muscle myosin heavy chain and consistent absence of a peripheral DOG1-positive layer around conventional invasive carcinoma. Nevertheless, focal loss in high-grade in-situ disease, occasional apical luminal staining, clone-dependent variation, and reduced sensitivity in true myoepithelial neoplasms prevent its use as a stand-alone determinant of invasion. Tumor-cell ANO1 expression represents a separate biological phenomenon and has shown heterogeneous associations with molecular subtype and prognosis.

Conclusion: DOG1 is best regarded as a complementary topographic marker within a morphology-led panel containing nuclear and cytoplasmic myoepithelial stains. Diagnostic interpretation should prioritize the location, continuity, and cellular identity of staining rather than positivity alone.

Keywords: DOG1; ANO1; myoepithelial cells; breast pathology; invasion

Introduction

Recognition of stromal invasion is one of the most consequential judgments in breast pathology. Benign epithelial proliferations and ductal carcinoma in situ (DCIS) are generally bounded by myoepithelial cells and basement membrane, whereas conventional invasive carcinoma breaches this epithelial-stromal barrier. The distinction affects staging, margin assessment, nodal evaluation, systemic treatment, and prognosis. In routine practice, however, invasion cannot be defined by the absence of one immunostain: myoepithelial cells may be attenuated in in-situ lesions, absent from selected non-invasive entities, or mimicked by tumor and stromal cells.[1,2]

Myoepithelial immunohistochemistry is therefore an adjunct to, rather than a replacement for, architectural assessment on hematoxylin and eosin sections. Diagnostic difficulty is greatest in sclerosing lesions, small glandular proliferations, papillary neoplasms, high-grade DCIS with inflammation, and limited core biopsies. In these settings, a panel should resolve a focused morphological question and be interpreted in its spatial context. Uncritical reliance on a single positive or negative stain can convert a technical or biological exception into an erroneous diagnosis.[1,3]

DOG1, initially developed as a marker of gastrointestinal stromal tumor, is an antibody surrogate for anoctamin-1 (ANO1/TMEM16A), a calcium-activated chloride channel. Its relatively crisp membranous-cytoplasmic labeling of mammary myoepithelial cells and limited staining of stromal myofibroblasts prompted investigation as a complementary breast marker. The same protein may also be expressed by neoplastic epithelial cells, creating an important conceptual distinction between peripheral myoepithelial DOG1 staining used to assess invasion and tumor-cell ANO1 expression studied as a biological or prognostic feature. This review integrates those two literatures while keeping their diagnostic meanings separate.[1,4]

The Myoepithelial Cell as a Diagnostic and Biological Interface

Normal mammary ducts and terminal duct lobular units contain luminal epithelial cells and an outer myoepithelial population resting on basement membrane. Ductal myoepithelial cells tend to form an elongated, near-continuous layer; lobular myoepithelial cells are more stellate and may appear discontinuous in a two-dimensional section. Their contractile phenotype is reflected by smooth-muscle proteins, while their epithelial lineage is demonstrated by basal cytokeratins and nuclear p63. This hybrid immunophenotype explains why different markers identify different cellular compartments and why no individual stain is uniformly sensitive and specific.[5,6]

Myoepithelial cells are not passive anatomical boundaries. They synthesize basement-membrane components, maintain epithelial polarity, regulate luminal differentiation, and produce protease inhibitors and paracrine mediators that can restrain invasion. During progression from normal epithelium to DCIS, the myoepithelial layer may remain morphologically recognizable but acquire altered gene expression and reduced tumor-suppressive function. Consequently, preservation of a stained rim establishes cellular topography more reliably than it establishes biological normality.[4,5]

The epithelial-stromal interface also contains basement membrane, collagen, inflammatory cells, vascular structures, and myofibroblasts. Desmoplasia, haphazard infiltration, fat entrapment, and irregular glands support invasion, but each feature has mimics. Conversely, rounded nests, circumscription, or basement-membrane-like material do not always exclude invasion. The strongest diagnosis combines low- and high-power architecture with the distribution of myoepithelial cells and basement membrane, rather than treating either component as an absolute binary rule.[2,3]

Conventional Myoepithelial Markers and Their Limitations

The most widely used markers fall into nuclear, smooth-muscle, and basal-epithelial groups. p63 provides sharply localized nuclear staining and avoids the extensive stromal background produced by several cytoplasmic markers. Its limitations include genuine discontinuity around some in-situ proliferations and focal expression by a subset of breast carcinomas. Smooth muscle myosin heavy chain (SMMHC) is generally sensitive and more specific than smooth muscle actin (SMA) or calponin, but it may label vessels and occasional stromal cells. Calponin and SMA are sensitive, yet myofibroblastic and vascular staining can simulate a peripheral layer in sclerotic tissue.[6,7]

DCIS-associated myoepithelial cells may lose or reduce individual antigens. Hilson et al. examined 101 DCIS cases and found reduced expression of at least one of seven markers in 84.2%; reduction was especially frequent for SMMHC and was more common in high-grade disease. This observation explains why a negative cytoplasmic marker around a suspicious focus does not by itself prove invasion and why combining markers that detect different cellular targets is more reliable than repeating similar smooth-muscle stains.[8]

Basal cytokeratins, CD10, S100, and D2-40 can supply additional evidence, but each introduces new ambiguity. Basal keratins may stain luminal cells in usual ductal hyperplasia and basal-like carcinoma; CD10 can label stromal cells; S100 is neither lineage-restricted nor consistently sensitive; and D2-40 may show patchy myoepithelial staining while highlighting lymphatic endothelium. Marker selection should therefore reflect the lesion under consideration, anticipated cross-reactivity, and the need for complementary nuclear and cytoplasmic localization.[1,6]

Table 1. Practical comparison of myoepithelial markers in breast pathology

Marker	Expected myoepithelial pattern	Main strength	Important pitfall	Practical role
p63	Nuclear	Crisp cellular localization with little vascular or myofibroblastic staining	May be discontinuous in DCIS; focal tumor-cell expression occurs	Preferred nuclear component of a panel[7]
SMMHC	Cytoplasmic	High sensitivity and better specificity than SMA/calponin in many settings	Vascular and occasional stromal staining; antigen loss in DCIS	Strong cytoplasmic partner for p63[7,8]
Calponin	Cytoplasmic	Sensitive, often forms a continuous rim	Frequent myofibroblast and smooth-muscle cross-reactivity	Useful when topography is clear; interpret with a nuclear stain[7]
SMA	Cytoplasmic	Highly sensitive and widely available	Extensive myofibroblastic, pericytic, and vascular staining	Screening marker; limited specificity in sclerotic lesions[6]
CK5/6 and other basal keratins	Cytoplasmic/membranous	Demonstrate basal epithelial phenotype	Luminal staining in usual hyperplasia and tumor-cell staining	Selected differential diagnoses, not a stand-alone invasion marker[1]
DOG1	Membranous and cytoplasmic	Distinct peripheral rim with little stromal or vascular staining	Focal loss in DCIS; occasional luminal or tumor-cell staining	Complementary marker when conventional stains are equivocal[1,9]

DOG1/ANO1: Molecular Identity and Staining Biology

DOG1 was discovered through gene-expression profiling of gastrointestinal stromal tumors and later identified as ANO1/TMEM16A, an eight-transmembrane calcium-activated chloride channel encoded at chromosome 11q13. ANO1 participates in chloride and bicarbonate transport, membrane excitability, epithelial secretion, and calcium-dependent signaling. The antibody recognizes protein expression rather than a lineage-specific transcriptional program; therefore, DOG1 positivity is not restricted to GIST or to myoepithelial cells.[9,10]

In the normal breast, DOG1 usually labels myoepithelial cells along ducts and lobules with membranous and cytoplasmic staining. The pattern may be continuous around ducts and more delicate around acini. Occasional luminal cells show weaker apical-luminal labeling, which is topographically different from the basal rim used to identify myoepithelium. Stromal myofibroblasts and vascular smooth muscle are usually negative or minimally reactive, offering a practical advantage over calponin and SMA in fibrotic tissue.[11]

Staining performance is influenced by clone, platform, fixation, antigen retrieval, dilution, and interpretive threshold. Published breast studies have used different antibodies and scoring approaches, making numerical sensitivity difficult to pool. A diagnostically useful result should reproduce appropriate internal controls in normal ducts or lobules on the same slide. Absence of both lesion staining and internal-control staining is technical failure, whereas preserved internal controls with focal lesional loss may represent a genuine biological alteration.[1,11]

Evidence Supporting DOG1 as a Breast Myoepithelial Marker

The most extensive dedicated study by Cheng et al. evaluated 210 breast specimens, including adenosis, in-situ carcinoma, invasive carcinoma, and selected epithelial-myoepithelial tumors. DOG1 labeled breast myoepithelial cells comparably to calponin, SMMHC, and p63. Forty-six of 50 in-situ carcinomas retained peripheral DOG1 staining, whereas the 60 conventional invasive carcinomas lacked a myoepithelial DOG1 rim. Four in-situ cases showed negligible staining, demonstrating both the diagnostic value and the non-absolute sensitivity of the marker.[11]

A 2022 Egyptian series evaluated 90 specimens divided equally among benign lesions, DCIS, and invasive carcinomas, with p63 and SMA as comparators. DOG1 highlighted myoepithelial cells in all benign and all DCIS cases, although staining intensity and extent varied, while all invasive carcinomas lacked peripheral staining. The complete separation reported in that cohort supports panel inclusion but should not be interpreted as universal test performance because case mix, sample size, and scoring thresholds influence accuracy.[12]

Perumandal et al. studied 60 breast lesions and found strong DOG1 expression in common benign proliferations, including fibroadenoma, ductal hyperplasia, and fibrocystic change, with strong negativity in malignant disease. DOG1 broadly paralleled p63 and showed little stromal or vascular noise. The study extends reproducibility across laboratories, but its grouping of lesions and modest sample size limit precise lesion-specific estimates, particularly for high-grade DCIS and diagnostically difficult special entities.[13]

These series are consistent in three clinically relevant respects: normal and benign myoepithelium usually expresses DOG1; most in-situ carcinomas retain a peripheral DOG1-positive layer; and conventional invasive carcinoma lacks that peripheral layer. Their limitations are equally consistent: retrospective or cross-sectional designs, heterogeneous clones and scoring, small numbers within individual diagnoses, and limited comparison with a prespecified multi-marker reference standard. DOG1 should therefore be characterized as a promising complementary marker rather than a validated replacement for established panels.[C11-C13]

Table 2. Principal studies evaluating DOG1 in human breast lesions

Study	Material	Comparator or design	Main DOG1 finding	Diagnostic interpretation
Cheng et al., 2016[11]	210 specimens; 50 in-situ and 60 invasive carcinomas plus benign and biphasic lesions	DOG1 compared with calponin, SMMHC, and p63	Peripheral DOG1 in 46/50 in-situ lesions; no myoepithelial rim in conventional invasive carcinomas	Strong evidence for panel use; focal false-negative in-situ staining remains possible
Abd El-Kareem et al., 2022[12]	90 specimens: 30 benign, 30 DCIS, 30 invasive	DOG1 with p63 and SMA	All benign and DCIS cases positive; all invasive cases lacked peripheral staining	Supports discriminatory value in a balanced cohort; external validation needed
Perumandal et al., 2023[13]	60 benign, non-invasive, and malignant lesions	DOG1 and p63	Strong benign expression and strong malignant negativity	Confirms reproducibility; limited lesion-specific precision
Jansen et al., 2021[14]	Tissue microarray of 15,965 tumors, including 1,002 breast carcinomas	Pan-tumor expression survey	Tumor-cell DOG1 occurred across many tumor types and was associated with ER expression in breast cancer	Demonstrates that tumor-cell positivity is not lineage-specific and must not be mistaken for a myoepithelial rim

Diagnostic Applications in Specific Breast Lesions

Adenosis and Small Glandular Proliferations

Sclerosing adenosis can mimic tubular carcinoma when compressed acini infiltrate dense stroma. Recognition of lobulocentric architecture, retained basement membrane, and a peripheral myoepithelial layer favors adenosis. DOG1 may delineate compressed myoepithelial cells with less stromal interference than SMA or calponin. The stain is most persuasive when it forms a basal rim around multiple glands and agrees with p63 or SMMHC; isolated granular or apical epithelial staining should not be counted as evidence of preserved myoepithelium.[15,16]

Microglandular adenosis is an important exception because its round glands characteristically lack myoepithelial cells despite being classified as a non-invasive proliferative lesion with recognized association with carcinoma. A negative DOG1 panel therefore cannot convert microglandular adenosis into invasive carcinoma. Triple-negative cytokeratin-positive, S100-positive glands with luminal secretions and basement membrane require integration of the characteristic phenotype and architecture. This exception illustrates why invasion is a morphological diagnosis informed, but not dictated, by myoepithelial staining.[2,3]

Ductal Carcinoma In Situ and Microinvasion

The main value of DOG1 in DCIS is demonstration of a residual peripheral layer around ducts expanded by atypical cells. High-grade DCIS may show inflammation, fibrosis, duct rupture, cancerization of lobules, and attenuated myoepithelium; all can produce irregular or absent staining. A small focus that lacks DOG1 but retains another myoepithelial marker is not invasive. Conversely, concordant loss of nuclear and cytoplasmic markers at a morphologically suspicious focus strengthens the diagnosis of microinvasion, especially when accompanied by stromal reaction and haphazard epithelial displacement.[8,17]

Interpretation on core biopsy requires additional restraint. Tangential sectioning can make an intact rim appear discontinuous, and tissue depletion across serial levels may cause different stains to evaluate different structures. Deeper levels, careful mapping of the suspicious focus, and markers applied to adjacent sections reduce this error. If the focus is minute and morphology remains equivocal, a descriptive diagnosis and excision recommendation may be safer than categorical overinterpretation based on one absent stain.[1,3]

Papillary Lesions

Papillary lesions are especially dependent on staining topography. Benign intraductal papilloma retains myoepithelial cells within fibrovascular cores and at the duct periphery. Atypical ductal proliferation or DCIS involving a papilloma may lose cells within involved fronds while preserving a peripheral layer. In contrast, papillary DCIS lacks myoepithelium within papillae but remains bounded peripherally. DOG1 can complement p63 in mapping these distributions, but the diagnostic question must specify whether staining is sought in the cores, at the outer wall, or both.[18]

Encapsulated and solid papillary carcinomas demonstrate why absence of a peripheral myoepithelial layer does not invariably predict conventional invasive behavior. Encapsulated papillary carcinoma often lacks both internal and peripheral myoepithelial cells yet is staged and managed according to its characteristic clinicopathological behavior unless frank invasion is present outside the capsule. Solid papillary carcinoma may similarly lack peripheral markers despite a circumscribed architecture. DOG1 negativity in these entities confirms absence of the layer but does not, by itself, establish invasion.[19,20]

Benign Sclerosing and Entrapped Epithelial Lesions

Radial scar, complex sclerosing lesion, nipple adenoma, and entrapped benign glands may show irregular outlines and apparent infiltration. A continuous DOG1-positive basal layer supports benignity, particularly when cytoplasmic smooth-muscle stains are obscured by reactive stroma. Nevertheless, patchy staining can occur because of section plane, compression, or antigen attenuation. Low-power architecture, elastosis, lobulocentricity, epithelial heterogeneity, and radiological-pathological concordance remain indispensable.[1,3]

Myoepithelial and Biphasic Neoplasms

Tumors with genuine myoepithelial differentiation require a different interpretive model. Adenomyoepithelioma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma contain neoplastic cells that may express p63, basal keratins, S100, SMA, calponin, or SMMHC. DOG1 is variably expressed and was insensitive in some biphasic tumors in the Cheng series. In this context, positivity indicates phenotype rather than a non-invasive boundary. Diagnosis depends on biphasic morphology and a coordinated lineage panel, not on transferring the invasion algorithm used for ordinary ductal lesions.[5,11]

Table 3. Context-specific interpretation of DOG1 staining

Diagnostic setting	Helpful DOG1 finding	Finding that requires caution	Recommended interpretation
Sclerosing adenosis vs tubular carcinoma	Peripheral basal rim around compressed glands	Patchy apical luminal staining	Confirm rim with p63 or SMMHC and lobulocentric morphology
DCIS vs invasive carcinoma	Preserved peripheral layer around involved ducts	Focal DOG1 loss in high-grade DCIS	Require concordant morphology and a second marker before diagnosing invasion
Suspected microinvasion	Concordant focal loss at a haphazard epithelial focus	Loss caused by duct rupture, inflammation, or tangential section	Examine deeper levels and adjacent sections; seek stromal response
Papillary lesion	Maps cells within cores and at the outer wall	Encapsulated/solid papillary carcinoma may lack a peripheral layer without conventional invasion	Interpret by lesion-specific criteria, not a universal binary rule
Microglandular adenosis	Usually confirms absence of myoepithelium	Negative result may mimic invasive carcinoma	Use architecture, S100, keratins, and basement membrane
Myoepithelial neoplasm	Tumor-cell staining can support phenotype	Variable sensitivity; positivity is not a preserved boundary	Apply a broad lineage panel and correlate with biphasic morphology

Major Interpretive Pitfalls

The first pitfall is failure to identify which cells are stained. True myoepithelial labeling is basal, peripheral, and geometrically related to a duct, lobule, or epithelial nest. Weak apical-luminal DOG1 staining does not form a barrier and should not be interpreted as myoepithelium. Diffuse labeling of carcinoma cells is a tumor phenotype. At low power, these patterns may appear similar; high-power correlation with nuclear position and the epithelial-stromal interface is necessary.[11,14]

The second pitfall is equating discontinuity with invasion. Normal lobules may appear discontinuous because their stellate myoepithelium is sampled obliquely, while DCIS-associated cells may downregulate markers. Technical variation also produces false loss. Internal controls, two mechanistically distinct markers, and examination of the same focus on adjacent levels are more informative than adding multiple stains that share the same source of cross-reactivity.[7,8]

The third pitfall is allowing immunohistochemistry to override lesion-specific biological evidence. Microglandular adenosis and selected papillary carcinomas are canonical examples of lesions that lack a conventional myoepithelial rim but are not classified solely by that absence. Conversely, invasive carcinomas may express p63, basal keratins, SMA, or DOG1 in tumor cells. The definition of invasion remains evidence of epithelial growth beyond the appropriate anatomical boundary in the context of the lesion being assessed.[2,17]

Tumor-Cell ANO1 Expression: A Separate Biological Signal

Tumor-cell ANO1 expression must be distinguished from peripheral myoepithelial DOG1. In a tissue-microarray survey of 15,965 tumors, DOG1 immunoreactivity occurred in 67 tumor types. Among 1,002 breast carcinomas, expression was associated with estrogen-receptor status but not with conventional measures of aggressiveness or prognosis. The breadth of tumor positivity reinforces that DOG1 is not lineage-specific when staining is diffuse within an epithelial neoplasm.[14]

Other breast studies have reported prognostic associations. Bae et al. examined 139 carcinomas and found that ANO1 expression correlated with β-catenin, cyclin D1, MMP9, Snail, and E-cadherin-related pathways and independently predicted shorter overall and relapse-free survival. ANO1 knockdown or pharmacological inhibition reduced proliferation and invasion in MCF7 and MDA-MB-231 cells, supporting a mechanistic link to cell-cycle progression and epithelial-mesenchymal transition.[21]

The literature is not uniform. Wu et al. demonstrated cell-specific effects according to ER, PR, and HER2 status, and earlier work associated ANO1 overexpression with favorable outcome in selected PR-positive or HER2-negative patients receiving tamoxifen. Experimental studies also connect ANO1 with EGFR/CaMK and EGFR/STAT3 signaling, but the magnitude and direction of effect vary by cellular context. These differences may reflect tumor subtype, antibody threshold, gene amplification, treatment exposure, channel activity, and non-channel scaffold functions.[C22-C25]

Accordingly, diagnostic and prognostic questions should not be conflated. A peripheral rim addresses whether myoepithelial cells surround a structure. Diffuse tumor-cell staining raises a research question about ANO1 biology and currently has no established role in routine breast prognostication or treatment selection. Candidate ANO1 inhibitors remain preclinical, and neither immunohistochemical positivity nor 11q13 amplification is presently sufficient to define a therapeutic population.[21,26]

A Practical Morphology-Led Approach

When invasion is uncertain, the pathologist should first define the exact focus and the competing diagnoses on H&E. The second step is to choose complementary stains: commonly p63 plus SMMHC, calponin, or DOG1. The third is to verify internal controls and inspect the location, continuity, and cellular identity of staining at high power. The final decision integrates architecture, stromal response, lesion-specific exceptions, and concordance across levels rather than reducing interpretation to positive versus negative.[1,2]

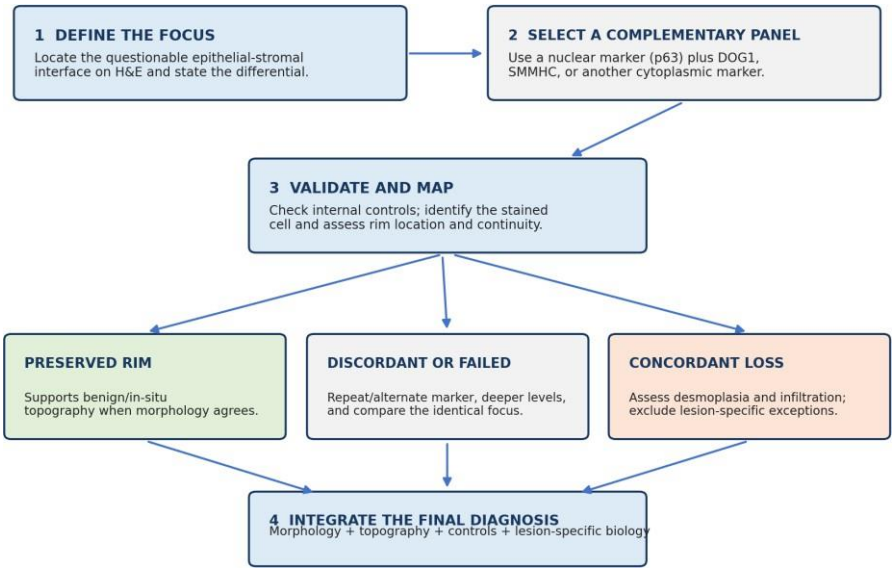

Figure 1. Morphology-led algorithm for using DOG1 in suspected breast invasion. DOG1 is positioned as a complementary cytoplasmic-membranous marker within a panel. The pathway separates technical failure, preserved myoepithelium, concordant loss, and recognized exceptions before a final diagnosis is made.[1,2]

Reporting need not list every stain when the result is straightforward, but difficult cases benefit from a concise interpretive statement. Examples include “DOG1 and p63 demonstrate a preserved peripheral myoepithelial layer, supporting an in-situ proliferation” or “the suspicious focus shows concordant loss of DOG1 and p63 with stromal desmoplasia, supporting invasion.” If stains are discordant, the report should state the limitation rather than imply certainty that the panel does not provide.[1,17]

Research Priorities

Future validation should use multicenter cohorts enriched for genuinely difficult lesions rather than easily separated benign and invasive extremes. Studies should prespecify clone, platform, fixation, scoring, reference standard, and lesion-specific outcomes. Comparative designs should include p63 and SMMHC, evaluate interobserver agreement, and report false-negative in-situ lesions and false-positive tumor-cell staining separately. Whole-section material is preferable to tissue microarrays for assessing continuity of a peripheral layer.[1,11]

Digital pathology may permit objective measurement of rim continuity, intensity, and spatial relationship to epithelial nests, but algorithms must be trained on the same exceptions that challenge human interpretation. A model that equates absent myoepithelial staining with invasion will systematically misclassify microglandular adenosis and selected papillary lesions. Molecular research should separately determine whether ANO1 channel activity, protein abundance, and 11q13 amplification identify reproducible breast-cancer subsets with therapeutic vulnerability.[14,26]

Strengths and Limitations

This review combines recent practical guidance on breast myoepithelial markers with the principal dedicated DOG1 breast studies and mechanistic ANO1 literature. The evidence base remains limited by small lesion-specific samples, heterogeneous antibodies and scoring systems, retrospective designs, and few direct head-to-head accuracy studies. Reported percentages should therefore not be pooled as if the studies used an identical test. The biological literature is also heterogeneous and does not yet support clinical prognostic or therapeutic use of tumor-cell ANO1.[C1,C11-C14]

Conclusion

DOG1 is a useful complementary myoepithelial marker in breast pathology, particularly when stromal cross-reactivity limits conventional cytoplasmic stains. Its diagnostic value arises from the spatial demonstration of a peripheral myoepithelial layer, not from positivity alone. Focal loss in DCIS, occasional luminal staining, true myoepithelial tumors, papillary exceptions, and technical variation prevent stand-alone interpretation. The most reliable approach remains morphology-led assessment supported by a nuclear and cytoplasmic-membranous panel. Diffuse tumor-cell ANO1 expression should be reported and studied as a separate biological phenomenon whose prognostic and therapeutic relevance remains unsettled.

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