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AGRI JOURNAL WORLD
VOL. 6 ISSUE 2 APRIL-JUNE, 2026

AQUAPORINS IN MAMMARY GLAND: EVOLVING TALE OF MASTOLOGY

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ABSTRACT

Aquaporins (AQPs) are membrane channel proteins that regulate water and small solute transport and are widely expressed in the mammary gland. Beyond maintaining fluid balance and lipid transport, aquaporin isoforms, including AQP1, AQP3, AQP4, AQP5, and AQP7, contribute to breast cancer progression by influencing cell proliferation, migration, invasion, angiogenesis, and epithelial–mesenchymal transition. Their expression is associated with tumor aggressiveness, microenvironment remodeling, and patient prognosis. Aquaporins show promise as diagnostic and prognostic biomarkers and potential therapeutic targets, although selective clinical inhibitors remain under development.

KEYWORDS: Aquaporins, biomarkers, breast cancer, mammary gland, tumor microenvironment

INTRODUCTION

Aquaporins (AQPs) are a family of small transmembrane channel proteins traditionally recognized for enabling rapid water transport across cell membranes, yet in mammary tissue they also govern glycerol and solute movement, thereby influencing local fluid balance and lipid metabolism. Over the past decade, studies in breast biology and oncology have shown that several aquaporin isoforms—particularly AQP1, AQP3, AQP4, AQP5 and AQP7—undergo a transition from purely physiological roles in the mammary gland to active modulation of cancer hallmarks, including proliferation, migration, invasion, angiogenesis and metastatic dissemination. Isoform- and cell-type-specific expression and localization patterns in endothelial cells, epithelial compartments, stromal fibroblasts and adipocytes have been correlated with tumor aggressiveness, remodelling of the tumor microenvironment and patient prognosis, positioning aquaporins as promising diagnostic and prognostic biomarkers as well as emerging therapeutic targets in breast cancer. In this article, we review the structural and functional characteristics of mammary aquaporins, delineate isoform-specific contributions to breast cancer progression and tumor–stroma crosstalk, and discuss current advances and remaining challenges in harnessing aquaporin-based strategies for early detection, risk stratification and targeted therapy in mastology.

AQUAPORINS

Aquaporins are small transmembrane proteins that form channels allowing water to move rapidly in and out of cells. They share a conserved structure: each aquaporin monomer has six alpha-helical segments crossing the cell membrane and two loops that fold into the membrane to form a narrow pore, and four monomers come together to form a functional tetramer. Functionally, aquaporins fall into two main groups. Water-selective aquaporins mainly transport water, while aquaglyceroporins also conduct glycerol and other small neutral solutes such as urea and some gases. This transport capacity is critical for processes like urine concentration, fat metabolism, brain water balance, and general cellular homeostasis.

At the molecular level, several structural motifs fine-tune channel function. Highly conserved NPA (Asn–Pro–Ala) motifs meet in the middle of the pore to control water permeability, while the aromatic/arginine (ar/R) region near the extracellular side acts as a selectivity filter based on size and charge. Changes in pH, phosphorylation, calcium, and hormones can open or close the channels or alter which molecules are transported, linking aquaporin activity tightly to the cell's environment.

FROM WATER CHANNELS TO CANCER DRIVERS

Over the last decade, the role of aquaporins in cancer biology has attracted intense interest. Studies in breast tissue have shown that many aquaporins are expressed both in normal mammary glands and in breast tumors, often with strikingly different patterns between healthy and malignant tissue. In normal adipose tissue, aquaglyceroporins such as AQP7 regulate glycerol flux, thereby influencing triglyceride storage, lipolysis, and overall energy balance. Dysregulation of these glycerol channels has been linked to obesity, insulin resistance, and altered lipid metabolism—conditions that themselves intersect with breast cancer risk and progression.

In breast cancer, specific aquaporin isoforms are associated with fundamental hallmarks of malignancy: uncontrolled proliferation, enhanced migration and invasion, angiogenesis, and metastatic spread. Expression analyses suggest that some aquaporins are upregulated (for example, AQP1, AQP8, AQP9 or AQP10 in certain datasets), while others such as AQP3, AQP4, AQP5, and AQP7 may be downregulated or mislocalized depending on tumor subtype and context. Importantly, protein localisation—where in the cell or tissue an aquaporin is expressed—often provides more prognostic information than mRNA levels alone.

ISOFORM-SPECIFIC ROLES IN BREAST CANCER

Although the aquaporin family is structurally related, individual members appear to have distinct roles in breast cancer biology.

Aquaporin-1 (AQP1)

AQP1 is typically found in endothelial cells and is strongly involved in angiogenesis. In breast tumours, higher AQP1 expression has been linked to increased microvessel density, more aggressive growth, and enhanced migration and invasion of cancer cells. In experimental models, depletion of AQP1 leads to abnormal tumor microvasculature and impaired tumour expansion.

Aquaporin-3 (AQP3)

AQP3 is an aquaglyceroporin expressed in many epithelial tissues, including mammary glands, where it supports glycerol transport and cellular hydration. In breast cancer cell lines such as MCF-7 and T47D, AQP3 promotes cell migration and invasion and regulates epithelial–mesenchymal transition (EMT)–related genes and cytoskeletal organisation. High AQP3 expression in estrogen receptor–positive tumors has been associated with poor differentiation and increased lymph node metastasis.

Aquaporin-4 (AQP4)

Better known for its role in the brain, AQP4 is also expressed in breast tissue. Silencing AQP4 in breast cancer cells reduces proliferation, migration, and invasion, while increasing E-cadherin expression, suggesting that AQP4 influences cell–cell adhesion and may modulate EMT and tissue architecture.

Aquaporin-5 (AQP5)

AQP5 has emerged as a prognostic marker in several cancers, including breast cancer. Its expression correlates with altered signaling through pathways such as Ras and Rac1 and with disruptions in epithelial cell–cell adhesion. Experimental knockdown of AQP5 reduces cell migration and proliferation, while overexpression in fibroblasts enhances their motility and can drive tumor formation, partly through activation of ERK signalling.

Aquaporin-7 (AQP7)

As a key glycerol channel in adipocytes, AQP7 links metabolism to cancer. In breast tumors, high AQP7 protein expression has been associated with poorer overall survival, and functional studies suggest that AQP7 promotes cell proliferation, modulates adhesion, and affects contact inhibition. Knockdown of

AQP7 reduces primary tumor burden and metastatic potential in experimental models, supporting its role as a negative prognostic marker.

Taken together, these findings position aquaporins not as passive channels but as active regulators of breast cancer behaviour, often integrating metabolic, structural, and signalling cues.

AQUAPORIN AND THE TUMOR MICROENVIRONMENT

Breast cancer does not develop in isolation; it arises within a complex tumor microenvironment composed of stromal fibroblasts, adipocytes, immune cells, extracellular matrix, and an often-abnormal vasculature. Aquaporins contribute to this microenvironment on several levels.

In fibroblasts, for example, overexpression of AQP5 increases motility and proliferation and supports tumor formation when these cells interact with cancer cells. This effect is coupled to activation of ERK1/2 signalling, illustrating how a water channel can modulate intracellular signalling cascades. Conversely, specific mutations in AQP5 can prevent tumor formation, highlighting the importance of precise structural features.

Mesenchymal stem cells within the tumor niche can promote breast cancer growth and angiogenesis by secreting cytokines and growth factors. Aquaporins expressed by both stromal and cancer cells likely help these cells adapt to hypoxic, nutrient-poor regions by facilitating water and solute flux, volume regulation, and possibly gas transport through central pores. Hypoxia and abnormal vascularisation—common features of solid tumors—can in turn modify aquaporin expression, creating feedback loops that support tumor survival and therapy resistance.

AQUAPORINS AS BIOMARKERS AND THERAPEUTIC TARGETS

Aquaporins' cell-type-specific expression and strong prognostic associations make them compelling candidates as both biomarkers and therapeutic targets in breast cancer. Distinct AQP expression profiles correlate with tumor subtype, grade, relapse-free survival and overall survival, and isoforms like AQP1 and AQP7 have been linked—depending on context—to either favourable or poor outcomes, supporting the idea of a multi-marker aquaporin panel to refine risk stratification and guide treatment choices.

Therapeutically, aquaporins can modulate chemosensitivity: for example, higher AQP1 expression in invasive ductal carcinoma has been associated with better response to anthracycline-based regimens, while experimental inhibition of AQP5 in colorectal cancer reduces proliferation and increases apoptosis, suggesting that similar approaches might benefit breast cancer. Despite this promise, translating

aquaporin biology into drugs is difficult because existing inhibitors are often poorly selective, hit multiple isoforms, and show significant off-target effects, making improved potency, selectivity and solubility urgent goals. A rational path forward is to test refined aquaporin inhibitors first as monotherapies in preclinical breast cancer models and then in combination with chemotherapy, endocrine therapy or targeted agents.

Overall, aquaporins have evolved from simple water channels to complex regulators at the intersection of membrane transport, metabolism, signalling, and tumor microenvironment interactions.

CONCLUSION

Aquaporins now stand out as promising, but still under-utilised, biomarkers and therapeutic targets in breast cancer, with isoform-specific expression patterns that can inform prognosis and treatment response. Going forward, mastology research should focus on validating aquaporin panels for early diagnosis and risk stratification, dissecting stromal versus tumor-cell contributions in different molecular subtypes, and designing highly selective aquaporin inhibitors that can be safely combined with standard systemic therapies.

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How to cite:

Jasmin, F. A. T. and Meena, S. (2026). Aquaporins in mammary gland: Evolving tale of mastology. Leaves and Dew Publication, New Delhi 110059. *Agri Journal World* 6 (2): 113-118.

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