



# Biomarkers derived from CmP signal network in triple negative breast cancers

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**Abstract:** Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related death in women, accounting for approximately 30% of all new cancer cases. The prognosis of breast cancer heavily depends on the stage of diagnosis, with early detection resulting in higher survival rates. Various risk factors, including family history, alcohol consumption and hormone exposure, contribute to breast cancer development. Triple-negative breast cancer (TNBC), characterized by the absence of certain receptors, is particularly aggressive and heterogeneous. Cerebral cavernous malformations (CCMs), abnormal dilations of small blood vessels in the brain, is contributed by mutated genes like *CCM1*, *CCM2*, and *CCM3* through the perturbed formation of the CCM signaling complex (CSC). The CSC-non-classic membrane progesterone receptors (mPRs)-progesterone (PRG) (CmP)/CSC-mPRs-PRG-classic nuclear progesterone receptors (nPRs) (CmPn) signaling network, which integrates the CSC with mPRs and nPRs, plays a role in breast cancer tumorigenesis. Understanding these pathways can provide insights into potential treatments. This paper focuses on the emerging field of CmPn/CmP signal networks, which involve PRG, its receptors (nPRs and mPRs), and the CSC. These networks play a role in tumorigenesis, particularly in TNBCs. Aims to deliver a thorough examination of the CmP/CmPn pathways concerning TNBCs, this paper provides a comprehensive overview of these pathways, explores their applications and highlights their significance in the context of TNBCs.

**Keywords:** Triple-negative breast cancer (TNBC); CCM signaling complex (CSC); prognostic biomarkers; CmP signal network; histological/molecular/immune subtypes of TNBCs

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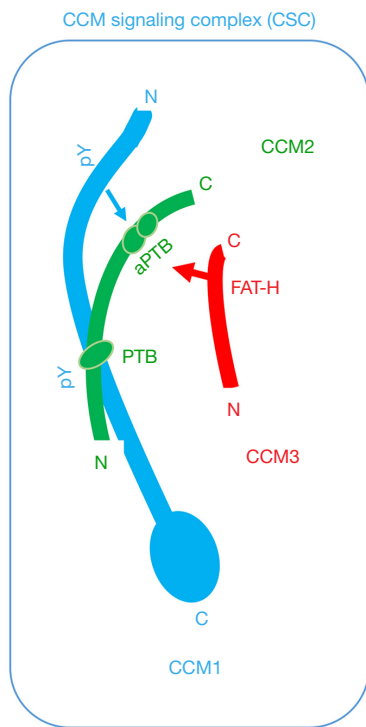
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## Introduction

Breast cancer is frequently detected and ranks second in terms of causing death among women due to cancer (1,2). It constitutes around 30% of all newly diagnosed cancer cases (3-8). The survival rates of breast cancer are greatly influenced by the stage at which it is diagnosed, with early detection leading to higher chances of survival (3,5,7). Multiple factors such as family history, alcohol

consumption, and hormone exposure play a role in the development of breast cancer (9-11). Triple-negative breast cancer (TNBC) is a highly aggressive and heterogeneous form of breast cancer, distinguished by the absence of three prominent receptors: estrogen receptor (ER), classic nuclear progesterone receptor (nPR), and receptor tyrosine-protein kinase erbB-2 (HER2) (12,13). TNBC is known for its significant heterogeneity, encompassing various histological,



**Figure 1** Schematic representation of binding interaction among CCM proteins within the CSC. Our current data suggests that CCM1 utilizes its pY to bind to CCM2 classic PTB. One of three CCM1 pY can also compete with the CCM3 (FAT-H) to bind to the aPTB of the CCM2, suggesting CCM2, as a scaffold protein, plays a central role in the CSC. CCM1: blue color; CCM2: light green color; CCM3: brown color. CCM, cerebral cavernous malformation; CSC, CCM signal complex; N, N-terminus; C, C-terminus; pY, NPXY motifs; PTB, phosphotyrosine binding domain; aPTB, atypical PTB domain; FAT-H, Focal Adhesion Targeting-Homology domain.

molecular, and immune subtypes that contribute to distinct clinical outcomes that are still not fully understood (14-16). Among TNBCs, over 70% are of basal phenotype, one of the most aggressive TNBCs, and non-classic membrane progesterone receptors (mPRs) role in tumorigenesis, especially in basal phenotype, is of great interest since basal phenotype-derived breast cancer cells do not express nPRs (17). The cerebral cavernous malformation signaling complex (CSC)-mPR-progesterone (PRG) (CmP)/CSC-mPR-PRG-nPR (CmPn) signaling network, which integrates the CSC with mPRs and nPRs, plays a role in breast cancer tumorigenesis. Understanding these pathways can provide insights into potential treatments. The involvement of mPRs in tumorigenesis is still under study, with initial beliefs suggesting their lack of genomic

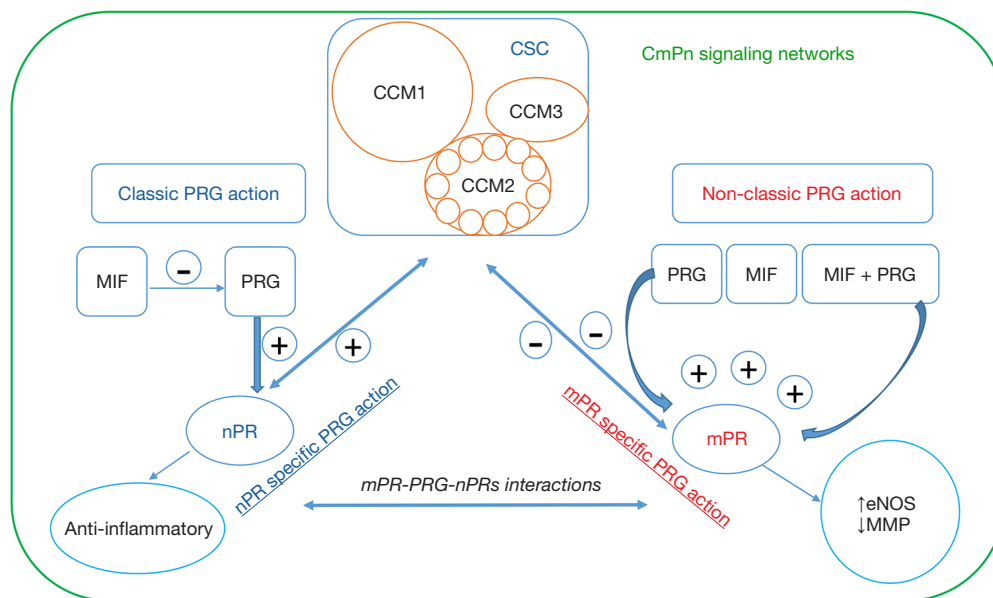
actions, but recent research has identified PRG receptors (PRs) throughout the cell. This paper aims to provide a comprehensive overview of the CmP/CmPn pathways and their significance in TNBC.

Cerebral cavernous malformations (CCMs) are abnormal dilations of small blood vessels in the brain, increasing the risk of stroke (18,19). Familial CCMs are hereditary and follow an autosomal dominant pattern (18-23). Deficiency of CCM1, CCM2, and CCM3 proteins, resulting from loss-of-function genetic mutations, contributes to this condition by disrupting the CSC (*Figure 1*) (20-23). Initially, PRG was thought to have a primary role in preparing the endometrium (24-26). Current understanding has reached a consensus that PRG can exert its effects through both classic and non-classic pathways, influencing the progression of breast cancer during tumorigenesis. It can independently bind to classic nuclear PRG receptors (nPRs) or non-classic mPRs, activating parallel signaling cascades (24-32). The CSC can modulate the interaction between mPRs and nPRs, merging these pathways into CmPn signal networks (*Figure 2*) (33). These signal networks are relevant in other types of tumorigenesis and vascular malformation during angiogenesis (8,33-40). The feedback regulation between PRG-mediated signaling and the CSC signaling within the CmPn signal network plays a crucial role in breast cancer development (41). Long-term exposure to PRG is associated with increased breast cancer risk (10), highlighting the significance of this network in tumorigenesis (8,33-40). Considering the influence of factors on the CmPn signaling network, various elements like trace minerals, antagonists, and agonists for PRs (mPRs/nPRs) have been considered for their potential application in breast cancer prevention and treatment (8,33-36,42-44).

This review aims to provide a concise overview of the signaling networks linked to the CmP/CmPn pathways and their involvement in the development of TNBC. Additionally, it presents an evolving understanding of the role of mPRs in tumorigenesis (8,33-36,42-45).

### Potential roles of CCM proteins in tumorigenesis

CCMs are characterized by abnormal dilation of small blood vessels in the brain, increasing the risk of stroke (18,19). This condition can be hereditary, following an autosomal dominant pattern of inheritance, and is associated with specific genes such as *CCM1*, *CCM2*, and *CCM3* (18-23). These genes encode proteins that interact with each other, forming the CSC (20-23). While the majority of



**Figure 2** Schematic diagram of mPR-specific PRG actions (PRG + MIF) within CmPn signal network. Within the CmPn signaling network, the CSC plays a regulatory role in modulating the interactions of PRG between nPRs and mPRs. This feedback regulation within the network involves the CSC acting as a modulator, influencing the channeling of PRG between nPRs and mPRs. CCM, cerebral cavernous malformation; CSC, CCM signal complex; PRG, progesterone; MIF, mifepristone; nPR, classic nuclear progesterone receptor; mPR, non-classic membrane progesterone receptor; eNOS, endothelial nitric oxide synthase; MMP, matrix metalloproteinase; CmPn, CSC-mPRs-PRG-nPRs.

research on CCMs has centered around their impact on cerebral cavernous hemangiomas and the increased risk of hemorrhagic stroke (20-23), there is emerging evidence indicating a potential involvement of CCM genes in tumor formation of major types of cancers (37). *CCM1*, one of the CCM genes, exhibits expression in various tissue types, indicating its diverse contribution to cellular physiology and its broader involvement in tumorigenesis across multiple tissues. This suggests that the CSC may play a role in tumorigenesis. While the full extent of these roles requires more research, there is strong suspicion that they significantly contribute to reproductive cancers, as evidenced by the increased expression of *CCM1* and *CCM3* correlating with higher severity and stages of endometrial tumors (37). The altered expression of CCM genes in liver disease and cancer, such as *CCM1* in early liver cirrhosis/hepatitis and stage one liver tumors, indicates a complex role in liver tumor development (37). Other members of the CSC, like *CCM2*, have also been observed in different types of tissues and cancers (46), including lymphomas, highlighting the intricate role of the CSC in tumorigenesis that requires further elucidation (37). These findings are

not unexpected, as studies have revealed that growing CCMs often coincide with mutations in the *PIK3CA* gene, which is commonly associated with cancer (47,48). The correlation between angiogenesis, shared genes implicated in tumorigenesis (47,48), and CCMs has provided insights into the possible role of CmPn signaling network in the development of both diseases.

### Inception of CmPn signaling networks

Originally, PRG was thought to primarily play a role in female reproductive systems, specifically in the preparation of the endometrium throughout pregnancies (24-26). However, current consensus acknowledges that PRG can influence breast cancer progression (27,29-32). It can independently bind to nPRs or mPRs, activating parallel signaling cascades (27-32). Previously, the CSC, which regulates microvascular integrity, was regarded as a distinct entity (20-23). However, recent studies have uncovered a connection between these formerly independent signaling pathways, as the CSC has the ability to modulate the interaction between mPRs and nPRs (33). This finding has led to the integration of these

three “independent” signaling cascades, giving rise to the complexes referred to as CmPn signal network (*Figure 2*) (33-36). This network is present in both nPR-positive cells, providing a comprehensive framework for understanding the interconnectedness of these pathways (8,33-40,49). The comprehension of mPRs’ role in tumorigenesis has undergone an evolving process, in contrast to the well-established classic nPRs. Initially, it was proposed that mPRs are a novel type of PRs that does not elicit genomic actions. However, several studies have identified PRs in different cellular locations, including the nucleus (41). The CmPn signaling network has been proven to play a crucial role in breast cancer development. Long-term exposure to PRG has been associated with an increased risk of breast cancer (10), further emphasizing the significance of this network in tumorigenesis (8,33-40). The discovery of the role of CmPn signaling network and tumorigenesis has sparked further investigation into their potential role in early detection. In summary, this section provides an overview of the present understanding of the signaling networks related to the CmPn network. It investigates the role of these signaling pathways in the development of TNBC and discusses potential applications for future treatment strategies.

### Factors influencing CmPn/CmP signaling networks

Considering the influence of some key factors on the CmPn signaling network, various elements like trace minerals, antagonists, and agonists for PRs for their potential application in breast cancer prevention and treatment. This section aims to provide a brief summary of the factors associated with the CmPn network, the shift from CmPn to CmP network in nPR(-) TNBC cells, and the significance of the CmP network in TNBC development. Furthermore, we will examine the possible application of these factors in forthcoming treatment strategies.

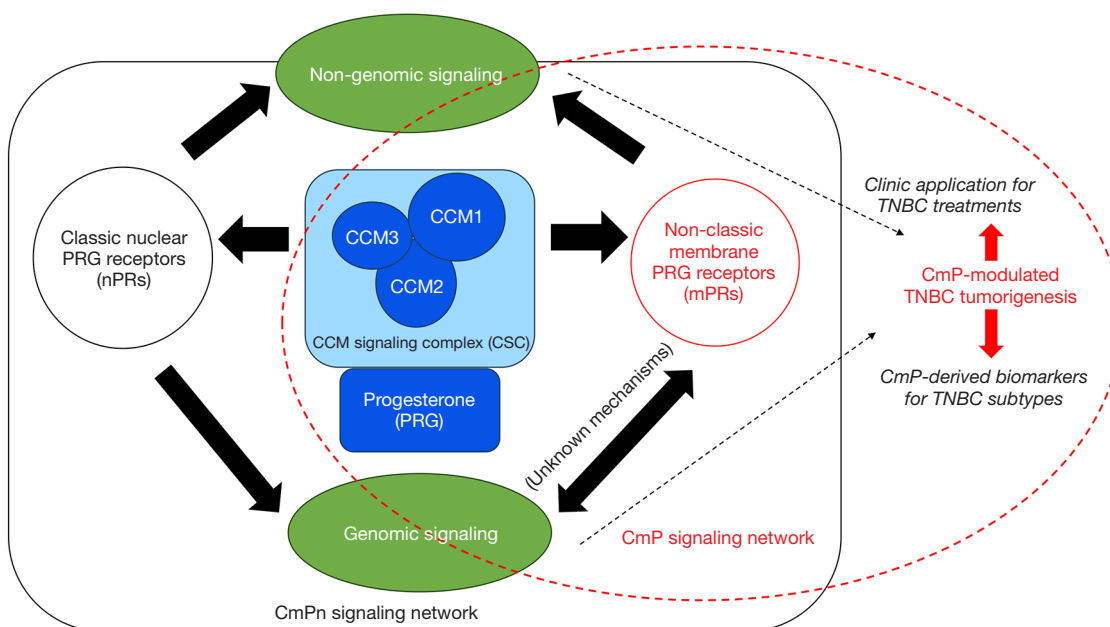
Mifepristone has demonstrated potential in reducing the growth of TNBC cell lines (42-45), which can be partly attributed to its mechanism of action within the CmP signaling pathway (8). Acting as both an antagonist for nPRs and an agonist for mPRs (42-45), mifepristone has shown the ability to suppress basal TNBC stem cells and inhibit the growth of both nPR(+/-) and nPR(-) TNBC cells in the presence of elevated levels of PRG (8,33-36,42-44). It is important to note that in nPR(-) TNBC cells, the combined effects of mifepristone and PRG specifically

target mPRs, working synergistically on these receptors. Using mifepristone to target breast cancer stem cells in TNBC has been identified as a treatment approach, opening up possibilities for exploring other functions within the CmP signaling cascade that could be targeted in future treatments (41,45). The ongoing investigation of the CmP pathway provides hope for the development of innovative therapeutic strategies for TNBC.

Zinc, an essential mineral with diverse physiological functions, plays a critical role in activating numerous enzymes in the body (8). It is involved in processes such as DNA synthesis, regulation of the female reproductive system, and maintenance of the immune system (50). Recent research has investigated the complex relationship between zinc and breast cancer development. Reduced zinc consumption has been linked to an increased risk of breast cancer, likely due to low levels of zinc between cells and elevated levels within cells (41). In the case of mutated mPRs, higher intracellular zinc levels facilitate the binding of PRG to mPRs, thereby restoring PRG’s ability to exert its effects within the cell (51). This finding provides insights into breast cancers that lack nPRs and highlights how PRG can still induce cellular mutations. The evidence of intracellular zinc enabling PRG binding through mPRs to influence CmP signaling network, presents challenges in the treatment of all nPR-negative cancers, particularly TNBC (8).

### Role of CmP in TNBC

TNBC is recognized as one of the most lethal types of breast cancer due to its aggressive nature and the absence of ER, PR, and HER2 expression (12,13). TNBC displays substantial heterogeneity, involving diverse histological, molecular, and immune subtypes that contribute to distinct clinical outcomes that are not yet fully comprehended (14-17). TNBC poses challenges for treatment due to its aggressive nature and lack of ER, nPRs, and HER2 expression (34,35). However, recent findings have shown that TNBC still interacts with PRG through non-classic membrane receptors (34,35). This discovery led to the identification of the novel hormone route known as the CmP, where PRG utilizes mPRs and the CSC to deliver PRG to the nuclear membrane (*Figure 3*) (34,35,41). Further research has confirmed the higher abundance of mPRs in TNBC compared to cancers with nPRs (34,35). This suggests that TNBC may receive continuous PRG signaling, creating an environment favorable for rapid



**Figure 3** CmP signal network-based biomarker discovery and therapeutic application. The depicted model showcases our current comprehension of the CmPn/CmP signal network’s role in breast cancer tumorigenesis, emphasizing the importance of mPRs in facilitating the continued influence of progesterone on both genomic and non-genomic actions. Investigating this network further holds potential for discovering innovative therapeutic strategies and prognostic biomarkers that specifically target the CmP signaling pathways in TNBC. nPRs, classic nuclear progesterone receptors; CCM, cerebral cavernous malformation; CSC, CCM signal complex; PRG, progesterone; mPRs, non-classic membrane progesterone receptors; TNBC, triple-negative breast cancer; CmP, CSC-mPRs-PRG; CmPn, CSC-mPRs-PRG-nPRs.

metastasis (8,33-36,38-40). These findings have also been supported by treatment options that have shown greater success in TNBC.

**Biomarkers discovered through CmP in TNBC**

Breast cancers exhibit significant clinical heterogeneity, and this variability is particularly prominent in TNBCs (52-55). TNBCs exhibit distinct variations in tumor aggressiveness, relapse rates, response to endocrine therapy, and sensitivity to cytotoxic chemotherapy (56-58). Hence, it is crucial to identify specific prognostic and predictive biomarkers unique to TNBC subtypes to guide clinical decision-making (59-62). Biomarkers, encompassing objectively measurable characteristics, play a vital role in predicting, diagnosing, prognosing, and assessing disease progression, regression, and treatment outcomes. Lehmann’s proposed sub-classification of TNBCs has demonstrated variability, ranging from seven to four subtypes, each with advantages and disadvantages based on the context Technological

advancements and expression profiling have significantly contributed to a more comprehensive characterization of TNBC subgroups, leading to the identification of precise biomarkers, therapeutic targets, and a better understanding of the underlying molecular mechanisms associated with TNBC (63-67). Tumor immune interactions in TNBCs are intricate and heterogeneous, influenced by diverse gene expressions within the tumor immune microenvironment. Various immune subtypes have been identified, impacting tumor-immune interactions and patient survival (68). Numerous biomarkers and signatures tailored to TNBC subtypes, addressing the challenges of immunotherapy, have been reported with prognostic value (16,69-73). Early detection of breast cancer is crucial for saving lives, and diagnostic and prognostic biomarkers play a pivotal role in achieving this goal (71,74-77). Biomarkers provide valuable information regarding cancer staging, location, and signaling cascades involved in cancer development (38,78-82). The discovery of novel biomarkers continues to advance our understanding of TNBC and holds promise

for improved diagnosis and treatment. While numerous biomarkers have been identified, it is important to recognize the potential of prognostic and etiological biomarkers for early detection and as targets for treatment options (34,83,84). These biomarkers hold the key to unlocking pathways that can be utilized for developing effective therapies (33-35,37,38).

### Alternative options

The current treatment options for TNBC are limited to chemotherapy, targeted agents, and immune checkpoint inhibitors, with chemotherapy being the standard approach (85). However, even with the introduction of targeted agents and immune checkpoint inhibitors, the overall survival rate for metastatic TNBC beyond 5 years remains at only 11% (86). In order to improve this outcome, it is crucial to explore alternative signaling cascades such as the CmP pathway, which holds potential for novel treatment strategies that have yet to be investigated (33-35,37,38). Notably, changes in *CCM* gene expression have been observed in reproductive cancers, including breast cancer, indicating a potential avenue for preventing tumor metastasis, which is associated with poor prognosis (34,35,37). Further research and understanding of the mechanisms involved in the CmP signaling cascade could lead to the identification of additional targeted therapies for future treatments, offering hope for improved outcomes in TNBC.

Investigating biomarkers derived from the CmP signal network holds promise for TNBC diagnosis and treatment. By analyzing the components of this network, researchers are able to identify specific molecular markers that can distinguish TNBC from other breast cancer subtypes. These biomarkers can provide valuable information about the prognosis and potential therapeutic targets for TNBC patients (34,35).

Additionally, understanding the dynamics and interactions within the CmP signal network can help identify novel therapeutic approaches. By targeting specific components of this network, such as mPRs or CSC, researchers may develop personalized treatments for TNBC patients. This approach could potentially improve patient outcomes and reduce the aggressiveness of this subtype.

### Conclusions

This review focuses on the development of diagnostic

and prognostic biomarkers in breast cancer, particularly in the context of TNBC. It highlights the importance of understanding the CmP signaling cascade and its associated factors in breast cancer tumorigenesis. The discovery of mPRs and the involvement of the CSC have provided new insights into the mechanisms underlying breast cancer progression. These findings contribute to the identification of prognostic biomarkers and the development of targeted therapies that interact with the CmP signaling cascade and its key components. The review emphasizes the potential of targeting various components of the CmP network, such as mPRs or CCM proteins, and utilizing biomarker-guided approaches to improve the prognosis and life expectancy of breast cancer patients and those with related conditions.

In summary, the exploration of biomarkers derived from the CmP signal network in TNBCs holds great promise for advancing our understanding of this aggressive subtype of breast cancer. By deciphering the intricate mechanisms within this network, researchers can potentially develop targeted therapies and improve patient outcomes in TNBC.

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