



RHOT1/RHOT2 in Prostate Cancer: Mitochondrial Trafficking, Stress Signaling, Invasion, and Therapeutic Opportunities

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ABSTRACT

Mitochondrial biology has emerged as an important determinant of cancer progression, encompassing not only oxidative metabolism and redox homeostasis but also mitochondrial dynamics, intracellular positioning, signaling, and communication with the cytoskeleton. RHOT1 and RHOT2, encoding the mitochondrial Rho GTPases MIRO1 and MIRO2, respectively, are outer mitochondrial membrane proteins that regulate mitochondrial trafficking and positioning. Although structurally related, accumulating evidence indicates that MIRO1 and MIRO2 can perform non-redundant functions in cancer. Among the two proteins, RHOT2/MIRO2 has the strongest direct evidence in prostate cancer (PCa). MIRO2 is overexpressed in advanced and metastatic PCa, is associated with adverse clinical outcomes, and promotes prostate cancer cell growth through a MIRO2–GCN1–ATF4 stress-signaling pathway. More recent work has established an additional role for MIRO2 in prostate cancer invasion and metastasis through interaction with unconventional myosin 9B (MYO9B) and suppression of RhoA activity. By contrast, direct evidence connecting RHOT1/MIRO1 to prostate tumorigenesis remains limited, and experimental depletion of MIRO1 did not reproduce the growth or stress-signaling phenotypes observed following MIRO2 depletion in PCa models. Nevertheless, MIRO1 has well-established roles in Ca²⁺-dependent mitochondrial trafficking, mitochondrial–cytoskeletal coupling, and intercellular mitochondrial transfer, providing several plausible mechanisms by which RHOT1 could influence PCa biology. This review summarizes the molecular biology of RHOT1/MIRO1 and RHOT2/MIRO2, evaluates their current evidence base in prostate cancer, discusses their connections with mitochondrial dynamics, metabolic stress, hypoxia, invasion and metastasis, and identifies major questions that must be addressed before MIRO proteins can be considered clinically actionable targets in PCa.

ARTICLE HISTORY

Received: Oct. 6, 2026

Revised: Oct. 9, 2026

Accepted: Oct. 9, 2026

KEYWORDS

RHOT1, RHOT2,
Mitochondria, Metastasis,
Prostate Cancer

1. Introduction

Prostate cancer is one of the most frequently diagnosed malignancies in men and remains a major cause of cancer-related mortality, particularly when disease progresses to metastatic or castration-resistant prostate cancer [1]. Although androgen-receptor (AR)-directed therapies have substantially improved outcomes, advanced PCa eventually develops adaptive mechanisms that allow tumor cells to survive androgen deprivation, metabolic stress, hypoxia, and therapeutic pressure [2, 3]. Mitochondria are increasingly recognized as central participants in these adaptations and provide ATP and biosynthetic intermediates, regulate reactive oxygen species and Ca²⁺, participate in apoptosis, and communicate extensively with other cellular compartments [4]. Importantly, mitochondrial function is determined not only by

biochemical activity but also by where mitochondria are located within the cell [5].

Mitochondrial positioning is controlled by a conserved trafficking apparatus involving the mitochondrial outer membrane proteins MIRO1 and MIRO2, cytoskeletal adaptor proteins such as TRAK1/2, and microtubule motors including kinesin and dynein [6, 7]. MIRO proteins therefore constitute an interface between mitochondria, the cytoskeleton, and intracellular signaling [8]. The mammalian genes encoding these proteins are RHOT1 (MIRO1) and RHOT2 (MIRO2). The proteins belong to the atypical mitochondrial Rho GTPase family and possess two GTPase domains, two Ca²⁺-binding EF-hand motifs, and a C-terminal transmembrane region that anchors them in the outer mitochondrial membrane [9].

The relevance of this machinery to cancer has become increasingly apparent. Tumor cells redistribute mitochondria to satisfy localized energetic and signaling requirements, particularly during migration, invasion, hypoxia, and metabolic stress [10]. Mitochondrial accumulation at the leading edge can support focal-adhesion turnover, membrane remodeling, and cell migration, while mitochondrial trafficking can also participate in intercellular mitochondrial transfer [11].

Within prostate cancer, however, the evidence for the two MIRO proteins is strikingly asymmetric. RHOT2/MIRO2 has been experimentally established as a regulator of prostate tumor growth and metastatic behavior [12], whereas evidence for RHOT1/MIRO1 is comparatively sparse [13]. This distinction is important because structural similarity between MIRO1 and MIRO2 does not imply functional redundancy in cancer. Indeed, experimental studies in PCa indicate that MIRO1 depletion does not reproduce the effects of MIRO2 depletion on tumor-cell growth, survival, or stress signaling [12].

2. Molecular biology of RHOT1 and RHOT2

2.1 MIRO1 and MIRO2 as mitochondrial trafficking proteins

MIRO1 and MIRO2 are highly conserved proteins of approximately 620 amino acids and share roughly 60% sequence homology [9]. Their distinctive architecture separates them from conventional Rho-family GTPases. Rather than functioning primarily as plasma-membrane signaling switches, MIRO proteins are embedded in the outer mitochondrial membrane through their C-terminal transmembrane domains [6]. Two GTPase domains flank a pair of EF-hand Ca^{2+} -binding motifs. The localization of mitochondria within the cell must be continuously adapted to local energetic and signaling requirements. MIRO proteins act as mitochondrial receptors/adaptors that connect mitochondria to motor-adaptor complexes. Early mechanistic studies demonstrated that MIRO1 interacts with the mitochondrial trafficking adaptor GRIF-1/TRAK and promotes kinesin-dependent mitochondrial transport [14].

MIRO1 additionally functions as a Ca^{2+} sensor. Changes in intracellular Ca^{2+} alter MIRO1-dependent mitochondrial motility, allowing mitochondria to be retained at sites where increased ATP production or Ca^{2+} buffering is required [15]. This provides

an important conceptual link between cellular signaling and mitochondrial positioning.

MIRO2 shares many of these canonical trafficking properties, but the two proteins should not be regarded as interchangeable. Cancer studies increasingly suggest that MIRO1 and MIRO2 can have distinct binding partners, stress responses and effects on tumor-cell phenotypes [6].

2.2 Mitochondrial trafficking and cancer

Cancer cells are highly dynamic systems in which mitochondrial localization can influence proliferation, migration, invasion, and survival. During migration, for example, mitochondria may become enriched at the leading edge to provide ATP and Ca^{2+} buffering required for focal-adhesion dynamics and cytoskeletal remodeling [5]. This phenomenon has particular relevance to prostate cancer because metastatic dissemination requires substantial changes in cell adhesion, motility, cytoskeletal organization, and metabolism. Consequently, mitochondrial trafficking proteins could affect tumor progression without necessarily changing total mitochondrial mass or respiratory capacity [16].

MIRO proteins may also participate in mitochondrial transfer through tunneling nanotubes and other forms of intercellular communication [17]. MIRO1 has been implicated in mitochondrial movement through cytoskeletal networks, while recent work has broadened the concept to RHOT1/2-dependent mitochondrial transfer between tumor and stromal cells [18]. The significance of this mechanism specifically in PCa remains an important area for future research.

3. RHOT2/MIRO2 in prostate cancer

3.1 MIRO2 expression and clinical association

The strongest current evidence concerning MIRO genes in PCa concerns RHOT2/MIRO2 [12, 13]. Furnish and colleagues examined MIRO2 expression in prostate cancer cohorts and found that MIRO2 mRNA was elevated in PCa compared with normal prostate tissue [13]. Importantly, MIRO2 expression was higher in metastatic or recurrent/progressed disease than in localized tumors, and elevated expression was associated with poorer patient survival [13]. Analysis of The Cancer Genome Atlas and additional prostate cancer datasets showed particularly interesting reciprocal behavior between the two MIRO genes. Whereas MIRO2 expression increased in PCa, MIRO1 did not exhibit the same ad-

verse prognostic relationship. The authors therefore investigated whether MIRO2 had a tumor-specific function rather than merely representing a redundant mitochondrial trafficking protein [13]. These observations are important for two reasons. First, they establish RHOT2 as a candidate biomarker associated with aggressive PCa. Second, they indicate that mitochondrial trafficking machinery may be transcriptionally or post-transcriptionally remodeled during prostate tumor progression. However, expression association alone does not establish causality. The subsequent functional studies are therefore particularly important.

3.2 *MIRO2 promotes prostate cancer cell growth*

In the seminal PCa study by Furnish et al., depletion of MIRO2 reduced prostate cancer cell growth and colony-forming capacity [13]. The phenotype was observed in models representing both androgen-sensitive and androgen-independent diseases. MIRO2 depletion also impaired tumor growth in mouse xenograft models [13]. These findings establish MIRO2 as more than a prognostic marker: the protein is functionally required for efficient tumor growth in experimental models. One of the most important aspects of the study was the demonstration that MIRO2 operates through a signaling mechanism distinct from its classical role in mitochondrial movement. Protein-interaction/network analysis identified General Control Nonderepressible 1 (GCN1) as a prominent MIRO2-associated protein. GCN1 is an important upstream regulator of the kinase GCN2, a central component of the integrated stress response (ISR) [13]. Thus, MIRO2 appears to act as a mitochondrial signaling platform connecting mitochondrial status to a cytosolic stress-response pathway.

4. The MIRO2–GCN1–GCN2–ATF4 axis

4.1 *GCN1 and GCN2 signaling*

The integrated stress response allows cells to adapt to conditions such as amino-acid deprivation, oxidative stress, hypoxia, and other disturbances in cellular homeostasis [19]. GCN1 functions as an upstream regulator of GCN2, while activated GCN2 phosphorylates eIF2 α , promoting selective translation of stress-responsive proteins, including activating transcription factor 4 (ATF4) [20]. ATF4 can then alter transcriptional programs controlling amino-acid metabolism, redox balance, protein homeostasis, and survival. This pathway is particularly

relevant to cancer because tumor cells frequently experience nutrient deprivation, hypoxia, and metabolic stress within poorly perfused tumor regions [21].

Furnish et al. demonstrated that MIRO2 is required for efficient GCN1-mediated GCN2 signaling in prostate cancer [13]. Loss of MIRO2 reduced activation of GCN2 and the downstream induction of ATF4. Importantly, the effects of MIRO2 on prostate cancer growth were mediated, at least in substantial part, through ATF4 [13]. This discovery substantially expands the biological significance of MIRO2. Rather than acting solely as a mitochondrial transport receptor, MIRO2 can function as a mitochondrial signaling regulator that enables cancer cells to translate metabolic stress into adaptive gene expression [13].

4.2 *Hypoxia and the tumor microenvironment*

Hypoxia is a characteristic feature of many solid tumors, including advanced prostate cancer [22]. Low oxygen availability restricts oxidative metabolism and can increase oxidative and metabolic stress, and cancer cells that successfully activate adaptive responses gain a survival advantage [23, 24]. In prostate cancer xenografts, MIRO2 and activated GCN2 were increased in hypoxic tumor regions. Their spatial correlation supports the hypothesis that MIRO2 helps tumor cells survive the hostile metabolic environment characteristic of poorly vascularized tumors [5, 13]. This provides a mechanistic explanation for why MIRO2 expression may become particularly relevant in advanced disease [5]. Metastatic tumors are not simply larger versions of localized tumors; they encounter different nutrients, oxygen, and stromal environments, and a mitochondrial protein capable of linking organelle biology to stress adaptation could therefore contribute to metastatic fitness [5].

5. MIRO2 and androgen signaling

Prostate cancer is fundamentally influenced by androgen receptor signaling, although advanced disease can become partially or completely androgen independent [25]. The observation that MIRO2 promotes growth in both androgen-sensitive and androgen-independent models is therefore significant [12, 13]. MIRO2 should not necessarily be viewed as a replacement for AR signaling. Rather, it may constitute a parallel survival pathway that enables tumor cells to tolerate metabolic and environmental stress regardless of their dependence on androgen signaling. The 2022 study explicitly concluded that MIRO2/GCN1/GCN2 signaling controls growth in

both androgen-independent and androgen-sensitive prostate cancer models [13]. This raises an important therapeutic hypothesis: MIRO2 inhibition could potentially complement AR-directed therapy by targeting an adaptive mitochondrial-stress pathway. Such a strategy might be especially relevant to tumors that retain AR activity but acquire enhanced metabolic plasticity [25, 26]. Nevertheless, this remains a preclinical hypothesis. There is currently no clinical evidence demonstrating that inhibition of RHOT2 improves response to androgen-deprivation therapy, androgen-receptor antagonists, or chemotherapy.

6. MIRO2 in prostate cancer invasion and metastasis

A major advance came from subsequent work demonstrating that MIRO2 is involved not only in primary tumor growth but also in invasion and metastasis. Boulton and colleagues reported that MIRO2 depletion reduced invasion in prostate cancer cells and decreased metastatic burden in mouse models. Their findings therefore extend the function of RHOT2 beyond proliferation and stress adaptation to the metastatic cascade [12]. The mechanism was particularly interesting because it involved MYO9B and RhoA, rather than simply mitochondrial trafficking [12].

MIRO2 interacts with unconventional myosin 9B (MYO9B), a motor protein with Rho GTPase-activating protein activity [6, 27]. Through this interaction, MIRO2 contributes to suppression of RhoA activity. Loss of MIRO2 increased active RhoA and impaired invasive behavior. Strikingly, simultaneous depletion of RhoA restored invasion in MIRO2-depleted cells, providing functional evidence that the MIRO2–MYO9B–RhoA pathway contributes directly to tumor-cell invasion [12]. The study demonstrated that this pathway operates in prostate as well as breast cancer models and that MIRO2 depletion reduces metastatic burden in vivo [6]. This is conceptually important because it demonstrates that a mitochondrial outer-membrane protein can regulate the cytoskeleton and cell invasion through a signaling complex involving a classical Rho-family GTPase.

7. RHOT1/MIRO1: what is known in prostate cancer?

In comparison with RHOT2, the evidence for RHOT1/MIRO1 in prostate cancer is limited. MIRO1 is a well-characterized regulator of mitochondrial trafficking [28]. It links mitochondria to

kinesin/dynein motor systems and functions as a Ca^{2+} -responsive regulator of mitochondrial positioning [14, 15]. Because mitochondrial localization is important for cancer-cell migration, energy production, and adaptation, RHOT1 is biologically plausible as a cancer regulator [6, 29]. MIRO1 has also been implicated in mitochondrial movement and intercellular mitochondrial transfer in other cancer contexts [17]. However, plausibility should not be confused with prostate-cancer-specific evidence. The most important comparative experiment comes from the PCa study by Furnish et al. [13]. Although the investigators examined MIRO1 because of the known functional overlap between MIRO1 and MIRO2, MIRO1 depletion did not reproduce the effects of MIRO2 loss on prostate cancer growth, survival, or stress signaling under nutrient-deprivation conditions [6]. This observation argues against a simple model in which RHOT1 and RHOT2 are interchangeable mitochondrial transport receptors in PCa. Instead, the available evidence favors a model of context-dependent functional specialization: 1) RHOT1/MIRO1 is strongly associated with canonical Ca^{2+} -regulated mitochondrial trafficking. 2) RHOT2/MIRO2 has a demonstrated role in PCa stress signaling. 3) RHOT2 additionally promotes prostate cancer invasion and metastasis through MYO9B/RhoA signaling. 4) The specific contribution of RHOT1 to PCa metabolism, therapy resistance, invasion, and metastasis remains insufficiently characterized. Consequently, future prostate cancer studies should avoid assuming that RHOT1 will phenocopy RHOT2.

8. Why might RHOT1 and RHOT2 behave differently?

The functional divergence between MIRO1 and MIRO2 is an important unresolved question [30]. One possibility is that the proteins have different interactomes. The two MIRO proteins share substantial sequence similarity but can interact with distinct regulatory proteins and signaling complexes [31]. The identification of GCN1 as a functionally important MIRO2-associated protein in PCa supports this concept [13]. A second possibility is differential regulation by cellular stress. Cancer cells experience conditions that are unusual compared with normal cells, including persistent hypoxia, nutrient limitation, altered Ca^{2+} signaling, oxidative stress, and cytoskeletal remodeling. MIRO2 may be preferentially engaged under some of these conditions. A third possibility involves subcellular localization. Although

both proteins are mitochondrial outer-membrane proteins, their interactions with motors, adaptors and signaling molecules may result in distinct mitochondrial pools. Finally, transcriptional regulation could differ between RHOT1 and RHOT2. Cancer-associated transcription factors may selectively regulate one MIRO gene. The broader cancer literature has implicated oncogenic transcriptional programs in regulation of mitochondrial trafficking, providing a potential mechanism for disease-specific induction of MIRO2 [6].

9. Integration with prostate cancer mitochondrial biology

The emerging role of MIRO proteins should be considered within the broader context of mitochondrial remodeling in PCa [32]. Prostate cancer cells undergo substantial changes in oxidative phosphorylation, lipid metabolism, mitochondrial dynamics, and redox regulation [33]. Androgen signaling can influence mitochondrial metabolism, while alterations in mitochondrial fission and fusion have been associated with PCa growth and stem-cell phenotypes [32].

MIRO2 adds a different dimension to this biology: mitochondrial positioning and signaling. A mitochondrion is not functionally equivalent regardless of its intracellular location. Mitochondria positioned near the plasma membrane, focal adhesions, endoplasmic reticulum, or nucleus can participate in different biochemical processes [34]. Consequently, changes in mitochondrial trafficking may affect tumor-cell behavior without major changes in total mitochondrial abundance [32]. The MIRO2 literature suggests at least three interconnected dimensions of mitochondrial regulation in PCa: 1) Stress adaptation: MIRO2 supports GCN1–ATF4 signaling. 2) Cytoskeletal regulation: MIRO2 interacts with MYO9B and influences RhoA activity. 3) Mitochondrial positioning: MIRO proteins provide the molecular interface between mitochondria and cytoskeletal transport machinery. These mechanisms could collectively promote tumor-cell survival and plasticity.

10. Potential therapeutic implications

The available evidence makes RHOT2/MIRO2 an intriguing therapeutic candidate, although several barriers remain.

10.1 Targeting MIRO2 directly

The simplest strategy would be pharmacological inhibition of MIRO2. In principle, disrupting its

mitochondrial signaling functions could impair tumor adaptation while sparing normal mitochondrial metabolism. However, MIRO proteins are important for normal mitochondrial physiology, particularly in neurons [30]. Therefore, systemic inhibition could produce neurological or other toxicity. A therapeutically useful MIRO2 inhibitor would need to exploit differences between tumor-associated and normal MIRO2 function.

10.2 Targeting the MIRO2–GCN1–GCN2–ATF4 pathway

An alternative approach would be to target downstream signaling. GCN1 or ATF4 inhibition could potentially reproduce some consequences of MIRO2 loss while avoiding direct inhibition of mitochondrial trafficking [13]. However, the ISR is also essential for normal stress adaptation, making therapeutic selectivity challenging [19]. Combination therapy could potentially provide greater specificity, for example by targeting MIRO2-dependent stress adaptation in tumors already metabolically stressed by AR-directed therapy.

10.3 Targeting MIRO2-dependent invasion

The MIRO2–MYO9B–RhoA pathway offers a separate therapeutic opportunity. Because this mechanism appears particularly relevant to invasion and metastasis, pathway inhibition might theoretically complement treatments that primarily control primary tumor growth [12]. The challenge is that Rho-family signaling is complex, highly interconnected, and important for normal cell physiology [35]. Directly targeting MIRO2 or its interaction with MYO9B could therefore be more selective than broadly suppressing RhoA.

11. RHOT1 and RHOT2 as potential biomarkers

RHOT2 currently has substantially stronger evidence than RHOT1 as a prognostic biomarker in PCa. Elevated MIRO2 expression has been associated with metastatic/recurrent disease and poorer survival, while MIRO2 protein has been detected in prostate tumor epithelium [13]. Nevertheless, several issues must be resolved before RHOT2 can be considered a clinically useful biomarker: 1) prospective validation in large independent cohorts; 2) assessment at the protein rather than solely transcript level; 3) determination of whether RHOT2 adds predictive value beyond PSA, Gleason grade, stage and established molecular biomarkers; 4) evaluation in castration-resistant and treatment-resistant disease;

5) assessment of whether RHOT2 predicts response to specific therapies. For RHOT1, there is currently insufficient evidence to recommend its use as a PCa biomarker.

12. Major knowledge gaps and future research directions

Several questions should guide future studies. First, the transcriptional regulation of RHOT2 in prostate cancer remains incompletely understood. It will be important to determine how AR signaling, MYC, hypoxia-inducible pathways, and other oncogenic transcription factors regulate RHOT2.

Second, the relationship between mitochondrial trafficking and MIRO2-dependent stress signaling needs clarification. The GCN1/GCN2/ATF4 pathway does not necessarily require active mitochondrial movement. Determining whether MIRO2's trafficking function is mechanistically connected to its signaling function will be critical.

Third, the relationship between RHOT2 and mitochondrial metabolism remains unresolved. Does MIRO2 alter oxidative phosphorylation, fatty-acid oxidation, ATP generation, or ROS production directly, or does it primarily reorganize mitochondrial localization and stress signaling?

Fourth, RHOT1 requires systematic investigation in PCa. CRISPR-based loss-of-function studies, rescue experiments with wild-type and mutant RHOT1, live-cell mitochondrial tracking, spatial proteomics, and metabolomics could establish whether MIRO1 has context-dependent functions that have not yet been detected.

Fifth, the metastatic role of MIRO2 deserves further study. The MYO9B/RhoA pathway establishes a link to invasion, but the relationship between this pathway and mitochondrial trafficking remains unknown. It is possible that MIRO2 simultaneously regulates mitochondrial localization and cytoskeletal signaling during metastatic dissemination.

Sixth, the tumor microenvironment should be incorporated into future studies. Cancer-associated fibroblasts, immune cells, and endothelial cells can exchange mitochondria with tumor cells. RHOT1/2-dependent mitochondrial transfer could therefore influence treatment resistance and metastatic fitness beyond tumor-cell-intrinsic mechanisms [17, 18].

13. Conclusions

RHOT1 and RHOT2 encode the mitochondrial Rho GTPases MIRO1 and MIRO2, proteins traditionally recognized for regulating mitochondrial trafficking through interactions with the cytoskeleton. Their emerging importance in cancer demonstrates that mitochondrial positioning is not merely a house-keeping process but can influence tumor signaling, stress adaptation, invasion, and metastasis. The current evidence in prostate cancer is strongly weighted toward RHOT2/MIRO2. MIRO2 is overexpressed in aggressive prostate cancer, correlates with adverse clinical outcomes, and promotes tumor growth through a MIRO2–GCN1–ATF4 signaling axis. Subsequent work has demonstrated that MIRO2 also promotes invasion and metastasis through interaction with MYO9B and suppression of RhoA activity [6, 12, 13]. Together, these findings position RHOT2 as a multifunctional regulator linking mitochondrial biology, stress adaptation, and cytoskeletal signaling.

In contrast, RHOT1/MIRO1 remains an underexplored component of prostate cancer biology. Although its established functions in Ca^{2+} sensing and mitochondrial trafficking make it an attractive candidate, direct PCa evidence is currently insufficient to assign RHOT1 a tumor-promoting or tumor-suppressive role. Indeed, existing comparative experiments suggest that RHOT1 and RHOT2 are functionally nonredundant in PCa [6, 18].

The most compelling future direction is therefore not simply to ask whether MIRO proteins regulate mitochondria in prostate cancer, but how specific MIRO-dependent mitochondrial signaling states allow prostate tumor cells to survive metabolic stress and acquire metastatic competence. Resolving this question could reveal new biomarkers and therapeutic vulnerabilities, particularly in advanced and treatment-resistant disease.

Declarations

Funding: This work is partially supported by the DOD PCRP PC230111 to Dr. Benyi Li.

Conflicts of Interest: The authors declare no conflicts of interest.

Data Availability: No new data was generated for this study.

Ethical Approval: Not applicable.

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