International Journal of Anesthesia and Clinical Medicine
2025, Vol. 13, No. 2, pp. 76-81
https://doi.org/10.11648/j.ijacm.20251302.13

Research Article

Research Advances in the Biological Functions of RBM3

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Abstract

In clinical research, "hypothermia therapy" (at 32-34 ℃) has been proven to be an effective method for alleviating neurological deficits in neonatal hypoxic-ischemic encephalopathy and adult acute brain injury. Even deeper levels of hypothermia have been used in heart and transplant surgeries. However, "hypothermia therapy" in clinical settings cannot avoid many life-threatening side effects. Its effects go far beyond what was initially observed under hypothermic conditions. RNA-binding motif protein 3 (RBM3), a critical cold shock protein, has revealed significance extending far beyond its initial discovery in hypothermia. Induced by diverse stressors-notably mild hypothermia-RBM3 orchestrates complex post-transcriptional processes, modulating mRNA stability, translation, alternative splicing, and phase separation. It further regulates multiple cellular physiological processes, including neuroprotection, tumorigenesis, anti-apoptosis, and cell cycle progression. This review outlines RBM3's structure and distribution in humans and synthesizes recent advances in understanding its multifaceted biological functions.

Keywords

RNA-Binding Motif Protein 3, Neuroprotection, Cancer

1. Introduction

Hibernating animals adapt to cold environments through tolerance to reduced blood flow, energy consumption, and body temperature while maintaining tissue oxygenation and metabolic homeostasis [1, 2]. Over the past two decades, studies identified that mammals produce specific proteins during hypothermia that decelerate cellular metabolism. Termed cold shock proteins (CSPs), these regulators influence cell proliferation, neuronal differentiation/maturation, axonal guidance, and synaptic remodeling [3-5]. RBM3 is a key CSP member. Clinically, therapeutic hypothermia (32-34 ℃) mitigates neurological deficits in neonatal hypoxic-ischemic encephalopathy [6] and adult acute brain injury [7], with deeper hypothermia used in cardiac and transplant surgeries [8]. However, this therapy carries life-threatening complications [9]. Thus, CSPs like RBM3 represent promising targets for mimicking hypothermia's benefits. Beyond cold adaptation, RBM3 exerts cytoprotective functions under endogenous and environmental stressors at normothermia [10] and participates in tumorigenesis [11]. This review summarizes recent advances in RBM3's biological roles.

2. Structural Features and Spatiotemporal Distribution of RBM3

RBM3, encoded on chromosome Xp11.2 [12], comprises 157 amino acids. Its N-terminus harbors two highly conserved RNA recognition motifs (RRM1 and RRM2), which

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Received: 21 July 2025; **Accepted:** 31 July 2025; **Published:** 13 August 2025

mediate RNA processing, splicing, export, stability, packaging, and degradation [55]. The C-terminal arginine-glycine-rich domain (RGG) governs protein localization, DNA damage response, mRNA translation, and synaptic plasticity [56], placing RBM3 within the glycine-rich protein (GRP) family.

As a cold shock protein, RBM3 is induced by hypothermia, hypoxia, and mild stress [13]. In mammals, RBM3 peaks neonatally but declines markedly in most brain regions during adulthood, except neurogenic niches like the subventricular (SVZ) and subgranular zones (SGZ) [14, 15]. The spatial distribution of RBM3 in major organs varies across species. In humans, RBM3 expression is minimal or absent in the thyroid and heart [16]. In hibernating animals, such as black bears and squirrels, RBM3 is upregulated in muscle, liver, and heart tissues [17-19]. At the subcellular level, RBM3 primarily localizes to the nucleus due to its RGG domain, which serves as a nuclear localization signal facilitating nucleocytoplasmic shuttling [20]. Within the nucleus, RBM3 regulates gene transcription or binds specific mRNAs for post-transcriptional modulation. Under physiological or stress conditions, RBM3 shuttles between the nucleus and cytoplasm to exert its biological functions [21].

3. Biological Functions of RBM3

3.1. Neuroprotection

Mild hypothermia's neuroprotective effects are closely linked to RBM3, It is mainly manifested in the following aspects:

1) RBM3 is highly expressed in immature mouse neurons and widely distributed.
2) Its mRNA/protein levels increase significantly in neurons at 32-34 ℃.
3) Higher RBM3 correlates with reduced neuronal apoptosis.
4) RBM3 knockdown diminishes neuroprotection.
5) Hypothermia-induced RBM3 upregulation or normothermic overexpression attenuates apoptosis [22].

Thus, RBM3 acts as a mediator of hypothermic neuroprotection and a potential therapeutic target to circumvent clinical complications.

In prion-diseased and Alzheimer's models, RBM3 overexpression preserves synaptic structure (dendritic spine density, synaptic protein levels) and function, prolongs survival, and ameliorates behavioral deficits and neuroinflammation [23]. Conversely, RBM3 knockout suppresses synaptogenesis and accelerates disease [24]. After acute brain/spinal cord injury, RBM3 redistributes spatiotemporally [25]. In rat spinal cord injury (SCI) models, RBM3-positive cells increase dynamically, peaking at 1 day [26] or 5 days [25] post-injury—discrepancies possibly arising from surgical variability. Both studies support RBM3 upregulation and its critical role in SCI. RBM3 overexpression promotes axonal regeneration and functional recovery in SCI models.

Although RBM3 is recognized as a potent neuroprotective protein, its mechanisms remain incompletely understood. RBM3 binds the 3'UTR of YAP1 mRNA to regulate YAP1 expression, coordinating neurogenesis during cold stress [28]. Bastide et al. found that RBM3 interacts with RTN3 mRNA, enhancing its expression. RTN3, as a downstream effector of RBM3, mediates neuroprotection [27]. Post hypoxic-ischemic brain injury, RBM3 stimulates neuronal differentiation in the SVZ and SGZ and promotes neural stem/progenitor cell proliferation via the IMP2-IGF2 pathway [29, 30]. Additionally, RBM3 modulates apoptosis through multiple pathways, such as inhibiting MAPK signaling to counteract rotenone-induced neurotoxicity [53] and suppressing PARP cleavage in hypothermia-mediated neuroprotection [15]. In summary, RBM3 plays a pivotal role in neuroprotection, warranting further investigation.

3.2. Cancer

RBM3 regulates protein synthesis and post-transcriptional gene expression, including RNA splicing, transport, surveillance, decay, and translation. Its expression correlates with tumor malignancy and staging, positioning it as a proto-oncogene in cancer development.

3.2.1. Colorectal Cancer

Colorectal cancer (CRC) is the fourth most common human malignancy. High RBM3 expression correlates with favorable CRC prognosis [31], while its loss associates with poor outcomes [32], suggesting RBM3 as a potential prognostic marker. Mechanistically, RBM3 upregulation in HCT116 and DLD1 colon cancer cells enhances β-catenin signaling via GSK3β activation, promoting cancer stem cell activity [33]. Thus, RBM3 is a promising therapeutic target in CRC.

3.2.2. Prostate Cancer

High RBM3 expression associates with poorly differentiated, aggressive tumors and independently predicts early recurrence [34]. RBM3 knockdown reduces cell viability and increases chemosensitivity [35], aligning with its pro-survival role. However, its prognostic value remains debated. One study showed RBM3 inhibits CD44 variant splicing, impairing cancer stemness and tumorigenesis [36]. These findings suggest cancer-type-specific RBM3 effects [37], necessitating further exploration.

3.2.3. Bladder Cancer

In urothelial bladder cancer, low RBM3 expression correlates with higher tumor grade and independently predicts reduced survival [38]. Elevated RBM3 associates with lower lymph node metastasis risk [39]. A small-scale study found RBM3 deficiency predicts poorer 5-year survival in early-stage patients [40].

3.2.4. Breast Cancer

RBM3 is overexpressed in breast cancer [41], where it modulates tumor progression via miRNA-mediated protein regulation [42]. X chromosome-linked RBM genes (RBMX, RBM3, RBM10) correlate with pro-apoptotic Bax expression [41]. While some studies link high RBM3 to favorable prognosis [43], others associate it with poor outcomes, possibly via ARPC2 3'UTR binding [44]. LncRNA-LINC0009 also regulates RBM3 to promote triple-negative breast cancer proliferation and invasion [45].

3.2.5. Other Cancers

In gastric cancer, high RBM3 correlates with reduced p53 expression and better prognosis [46]. In melanoma, metastatic tumors show RBM3 downregulation, while nuclear RBM3 in primary tumors associates with prolonged survival [47]. RBM3 inversely correlates with MCM3, a poor prognostic marker, further supporting its favorable role [48].

Overall, most studies position RBM3 as a favorable prognostic biomarker across cancers. However, conflicting findings underscore the need for further research into its tumor-specific roles.

3.3. Other Functions

3.3.1. Apoptosis Regulation

Early studies showed hypothermia (32 ℃) induces RBM3, protecting neurons from toxicant-induced apoptosis [15]. In breast cancer, RBM3 correlates with Bax expression [41]. Ferry et al. reported RBM3 overexpression inhibits apoptosis and necrosis in myoblasts, enhancing cell survival [49], suggesting therapeutic potential in muscle atrophy. Under serum starvation, RBM3 rescues apoptosis by restoring translation efficiency [16]. Feng et al. found RBM3 increases survival of LPS-treated pulmonary microvascular endothelial cells [50].

Mechanistically, RBM3 binds NF90 to suppress PERK-eIF2α-CHOP signaling, mitigating ER stress-induced apoptosis [51]. It also upregulates Bcl-2 and inhibits caspases [49] and blocks UV-induced p38/JNK activation [52]. Collectively, RBM3 exerts cytoprotection across cell types.

3.3.2. mRNA Transcription and Translation

RBM3 binds and modulates mRNA translation, notably stabilizing COX-2, IL-8, and VEGF mRNAs [54]. It enhances translation via:

1) RNA-independent binding to 60S ribosomal subunits;
2) Increasing polysome formation;
3) Promoting eIF4E phosphorylation [56];
4) RBM3 also regulates translation via microRNAs.

3.3.3. MicroRNA Biogenesis

Hypothermia-induced RBM3 alters miRNA levels to promote translation. It binds 70-nt pre-miRNAs, broadly regulating miRNA processing via Dicer [58]. Paradoxically, RBM3 knockdown upregulates thermosensitive immune-related miRNAs, preventing hyperthermia pathology [59]. While RBM3's miRNA regulatory role is clear, precise mechanisms require further study.

3.3.4. Cell Cycle

RBM3 regulates G2/M transition, linking it to tumor biology. RBM3 knockout induces mitotic defects in NIH3T3 fibroblasts and HCT116 cells [57]. RBM3-deficient mouse embryonic fibroblasts exhibit G2 arrest [60], confirming its necessity for mitosis. This may explain why RBM3-high tumors show better chemosensitivity and prognosis [61].

3.3.5. Inflammation

High circulating RBM3 reduces systemic inflammation during extracorporeal circulation [62]. In murine acute lung injury models, RBM3 overexpression enhances endothelial cell survival post-LPS but disrupts tight junctions [50]. RBM3 knockout exacerbates sepsis-induced lung injury and mortality via NF-κB/NLRP3 [63], highlighting its emerging role in inflammation.

4. Summary

This review outlines RBM3's roles in neuroprotection, cancer, apoptosis, mRNA regulation, cell cycle, and inflammation. As a cold shock protein, RBM3's neuroprotective effects are well-documented but require clinical validation. Before targeting RBM3 for hypothermia-mimetic therapies, further clinical studies are needed.

In cancer, RBM3's duality as both a favorable and unfavorable prognostic marker necessitates deeper exploration of its stage- and context-dependent roles. Its anti-apoptotic and cell cycle functions intersect with neuroprotection and tumorigenesis, positioning RBM3 as a multifaceted "protective molecule." Emerging roles in inflammation underscore its therapeutic potential. Elucidating RBM3's precise mechanisms and signaling pathways may pave the way for personalized therapies across diverse diseases.

Abbreviations

RBM3	RNA-Binding Motif Protein 3
CSPs	Cold Shock Proteins
RRM	RNA Recognition Motifs
GRP	Glycine-Rich Protein
SVZ	Subventricular
SGZ	Subgranular Zones
SCI	Spinal Cord Injury
CRC	Colorectal Cancer

Author Contributions

Feiyu Long is the sole author. The author read and approved the final manuscript.

Conflicts of Interest

The author declares no conflicts of interest.

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