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REVIEW

The Role of Cavin3 in the Development of Malignant Tumors

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Abstract: Cavin3, also known as PRKCDBP or SRBC, is an important member of the Cavin family. It plays a crucial role in the formation and functional regulation of caveolae while also acting as a tumor suppressor in the occurrence and development of most malignant tumors, primarily regulated by promoter region methylation. This paper systematically reviews the research progress of Cavin3 in breast cancer, lung cancer, gastric cancer, colorectal cancer and gynecological tumors, focusing on the role of Cavin3 in tumor prognosis and its possible regulatory mechanism. Current studies have shown that in breast cancer and lung cancer, Cavin3 can exert anti-tumor effects by inhibiting the PI3K/AKT signaling pathway and participating in DNA damage repair. In gastric cancer, it mainly activates downstream pathways by stabilizing p53, inducing cell cycle arrest and apoptosis. However, the specific role of Cavin3 in other tumor types and its broader regulatory mechanism have not yet been fully clarified and further in-depth research is needed. Future research on Cavin3 may provide new insights and effective strategies for precision diagnosis and treatment of malignant tumors.

Keywords: Cavin3, tumor suppressor, biomarker, signaling pathway

Introduction

Caveolae, as specialized microdomains on the plasma membrane, play an important role in biological processes such as cell signal transduction, lipid metabolism, and endocytosis.[1,2] As key molecules in the formation and functional regulation of caveolae, the cavin family has attracted increasing attention in recent years.[3] The family includes four subtypes: Cavin1 (PTRF), Cavin2 (SDPR), Cavin3 (PRKCDBP, SRBC) and Cavin4 (MURC), which play a synergistic role in the formation and functional regulation of mammalian cell membrane caveolae.[4,5] Among them, Cavin3, also known as PRKCDBP or SRBC, is an important member of this family. It is not only involved in the formation and stability of caveolae, but also plays an important regulatory role in the occurrence and development of various malignant tumors.[6,7] Cavin3 was originally identified as a protein kinase Cδ (PKCδ) binding protein,[8] located within the chromosomal 11p15.5-p15.4 region. One of its structural features is that it contains proline-rich regions at both the N-and C-terminal domains. Single-molecule imaging studies reveal that Cavin3 forms nanoclusters of approximately 50 nm in diameter with Caveolin 1 via an N-terminal helical structural domain, the absence of which leads to cell membrane abnormalities.[9] In addition to maintaining the structural stability of the cell membrane, it also plays an important regulatory role in cell signal transduction, endocytosis, cell metabolism and cell stress response.[5,10]

Currently, significant progress has been made in the study of the mechanism of action of Cavin3 in the occurrence and development of tumors. Studies have found that Cavin3 expression is significantly downregulated in a variety of malignant tumor tissues, suggesting that it may have a tumor-suppressing function.[11–14] At the molecular mechanism level, Cavin3 exerts its anti-tumor effects by regulating multiple key tumor-related signaling pathways. First, Cavin3 negatively regulates the PI3K/AKT/mTOR signaling pathway, inhibiting the proliferation and survival of tumor cells.[7]

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Second, Cavin3 plays an important regulatory role in the MAPK/ERK signaling pathway. Studies by Hernandez et al have shown that Cavin3 deficiency leads to sustained activation of the ERK signaling pathway, while Cavin3 re-expression can inhibit ERK phosphorylation and weaken downstream signal transduction, thereby inhibiting tumor cell proliferation and growth.[15] Lee et al[16] found that Cavin3 inhibits the proliferation of colorectal cancer cells by affecting the expression and activity of p53 and p21, leading to cell cycle arrest at the G1 phase.In terms of tumor cell apoptosis, Cavin3 can enhance TNF-α-induced apoptosis signals and promote the activation of Caspase-3 and Caspase-8, thereby enhancing tumor cell apoptosis.[16] In addition, Cavin3 may affect the tolerance of cancer cells to DNA damage and apoptosis by regulating DNA damage repair-related signals such as γH2AX phosphorylation.[8] This suggests that Cavin3 may have potential clinical application value as a tumor biomarker. Previous studies have found that Cavin3 promoter methylation is closely related to the occurrence and development of certain tumors and may serve as a molecular marker for early diagnosis of tumors. Epigenetic drugs targeting Cavin3 promoter methylation (eg 5-Aza-2′-deoxycytidine) have been studied in colorectal and lung cancer to restore its expression and enhance the sensitivity of tumor cells to chemotherapy (eg oxaliplatin).[16,17] However, small molecule inhibitors targeting Cavin3-related pathways are still in the exploratory stage, and future studies can further develop therapeutic strategies targeting Cavin3 and its downstream effector molecules.

Although the research on Cavin3 in tumors has gradually increased, there is currently a lack of systematic research on the mechanism and regulation of Cavin3 in different malignant tumors. The differences in the regulatory mechanism of Cavin3 in different tumor microenvironments, its functional synergy with other Cavin family members, and its potential role in tumor immunoregulation are still unclear. Future research should focus on clarifying the mechanism of action of Cavin3 in tumor metabolism and exploring precise treatment strategies targeting Cavin3. This review aims to comprehensively summarize the research progress of Cavin3 in lung cancer, breast cancer, digestive system tumors and other malignant tumors, deeply analyze its molecular mechanism and regulatory network, and explore its potential application value in tumor diagnosis and treatment, in order to provide new ideas for related basic research and clinical transformation.

Role of Cavin3 in Breast Cancer

Breast cancer is a highly heterogeneous disease that can be divided into multiple subtypes based on molecular characteristics. Xu et al[6] found through Western blot analysis that Cavin3 protein expression was not detected in approximately 70% of breast cancer and lung cancer cell lines. Its tumor suppressor function exhibits significant subtype-specific regulatory characteristics in breast cancer. Compared with normal breast tissue, Cavin3 mRNA levels were significantly reduced in patients with estrogen receptor-positive breast cancer, and its low expression was associated with an increased risk of lymph node metastasis and shortened overall survival. It is worth noting that in a cohort of 407 early breast cancer patients, Cavin3 protein expression was positively correlated with disease-free survival (DMFS) and overall survival (OS),[11] suggesting that Cavin3 expression levels may become an important indicator for the prognostic assessment of breast cancer patients,[18] and that it can serve as an independent prognostic marker for estrogen receptor-positive breast cancer subtypes.

Further mechanistic studies found that overexpression of Cavin3 can significantly inhibit the invasive ability of breast cells (MCF7, MDA-MB-231) and reduce the phosphorylation level of AKT, which may inhibit the downstream mTORC1 signaling. This effect is particularly significant in PTEN-deficient breast cancer. In addition, low Cavin3 expression may lead to overactivation of the PI3K/Akt signaling pathway and promote tumor progression.[11] In breast cancer, in addition to exerting its effects through the PI3K/Akt pathway, Cavin3 can also be released from caveolae under DNA damage stress, and directly interact with the BRCT domain of BRCA1 through the N-terminal domain, synergistically regulating the DNA damage repair signaling pathway, enhancing the efficiency of homologous recombination repair, and thus regulating the cell stress response. This study provides new ideas for targeted therapy.[5,19,20] The discovery of the mechanism by which Cavin3 regulates breast cancer through dual pathways provides important clues for understanding the role of Cavin3 in the progression of breast cancer and provides potential targets for developing new therapeutic strategies.

Role of Cavin3 in Lung Cancer

In lung cancer, protein level studies have found that the expression level of Cavin3 in lung cancer tissue is significantly lower than that in adjacent normal lung tissue.[6,17] Xu et al[6] first reported that Cavin3 expression was downregulated in lung cancer cell lines. Using Western blot analysis, they found that 26 out of 32 lung cancer cell lines (approximately 81%) had lost Cavin3 protein expression. This finding was subsequently confirmed by Zöchbauer-Müller et al in a study with a larger sample size.[17] They found that Cavin3 expression was significantly reduced or lost in approximately 76% of non-small cell lung cancer specimens, and hypermethylation of the gene promoter region was present in 41% of the samples. Loss of protein expression was observed in all samples where methylation was detected. Promoter methylation is an important mechanism leading to downregulation of Cavin3 expression, but low Cavin3 expression may also be affected by other factors, such as histone modification, miRNA-mediated transcriptional repression, or chromosome deletion.

The regulatory mechanism of Cavin3 in lung adenocarcinoma cells is different from that in breast cancer. First, certain compounds, such as Matrine, can induce apoptosis and autophagy in lung adenocarcinoma cells by upregulating Cavin3 expression,[13] a process closely associated with the inhibition of the PI3K/AKT signaling pathway.[21] This suggests that upregulating Cavin3 expression through natural compounds such as ephedrine may be a potential therapeutic strategy for lung adenocarcinoma.Second, Cavin3 enhances the stability of the p53 protein and promotes cell apoptosis by activating p53 function. Hypermethylation of Cavin3 leads to downregulation of p53, weakening its pro-apoptotic effects and promoting the progression of malignant tumors.[22] Moreover, Cavin3's interaction with various receptor tyrosine kinase (RTK) signaling pathways in lung adenocarcinoma cells plays a crucial role in maintaining vesicle formation and promoting cell survival signaling. For instance, ROR1, a transcriptional target, interacts with Cavin3 and is essential for caveolae-dependent endocytosis and survival signaling in lung adenocarcinoma cells. Studies have shown that after ROR1 binds to Cavin3, it promotes caveolae-dependent endocytosis and enhances the survival and proliferation activity of tumor cells by activating the PI3K/Akt signaling pathway. This interaction also inhibits cell apoptosis, further supporting tumor growth and metastasis.[23] In summary, Cavin3 plays a key role in regulating apoptosis and autophagy in lung adenocarcinoma cells and impacts cell survival signaling through interactions with RTK pathways. Future studies may focus on inhibiting the multiple scaffold functions of ROR1. The ROR1-Cavin3 complex may become a new target for the treatment of lung adenocarcinoma, in order to reduce the mortality rate of lung cancer and provide new strategies and ideas for the treatment of lung adenocarcinoma.

Role of Cavin3 in Digestive Tract Tumors

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer-related death worldwide.[24] Lee et al[25] first reported the abnormal expression and function of Cavin3 in gastric cancer. Through the analysis of gastric cancer tissue samples, researchers found that the expression of Cavin3 was significantly downregulated in 73% of gastric cancer cell lines and 41% of primary gastric tumors, and this downregulation was closely related to the hypermethylation of its promoter region.[25] Its main mechanism of action is to stabilize p53, activate the p21Waf1/PUMA/NOXA pathway, induce cell cycle arrest and apoptosis, and enhance the sensitivity of tumor cells to DNA damage stress. In addition, it may be involved in tumor suppression and proliferation regulation through the PKC-δ pathway.[25] Compared to breast cancer and lung cancer, the presence of Cavin3 in gastric cancer not only affects the proliferation and migration of tumor cells and the stability of the p53 protein, but also promotes tumorigenesis by altering the tumor microenvironment, including inflammatory responses and immune escape.[18,25,26] These findings provide theoretical support for Cavin3 as a cancer treatment target and biomarker, and future studies can further explore therapeutic strategies to restore Cavin3 function.

In colorectal cancer, Cavin3 also functions as a tumor suppressor gene. However, unlike in other tumors, Cavin3 primarily exerts its role through epigenetic changes in colorectal cancer, with Cavin3 CpG islands methylation-related silencing playing a crucial part.[16,17] Catia Moutinho et al has discovered that the resistance of colorectal cancer cells to the chemotherapy drug oxaliplatin is linked to Cavin3. This finding opens the door to addressing the issue of

chemotherapy resistance in colorectal cancer. In future studies, Cavin3 methylation can serve as a biomarker to predict drug sensitivity in colorectal cancer.[27]

Role of Cavin3 in Gynecological Tumors

There are relatively few studies on Cavin3 in gynecological tumors. Similar to other cancers, Cavin3 expression is reduced in ovarian cancer, which is primarily associated with the hypermethylation of the Cavin3 promoter region.[6,7,28]

In endometrial cancer, SEO-YUN TONG et al[29] were the first to demonstrate that Cavin3 expression differed between the tissue cells of endometrial cancer patients and the tissue cells of healthy women. They also discovered that Cavin3 could influence the histopathological characteristics of endometrial cancer. That is, the occurrence of endometrial cancer was closely associated with low expression of Cavin3, although the specific mechanism remains unclear.

In cervical cancer, LI et al[30] screened out four mRNAs (OPN3, DAAM2, HENMT1 and Cavin3) that were significantly correlated with prognosis through multivariate Cox regression analysis, and constructed a prognostic marker model based on these mRNAs. The area under the curve (AUC) of this model was 0.726, indicating that it has good prognostic assessment ability, but the specific mechanism is still unclear.It was also found that the expression of Cavin3 mRNA in tumor tissues was significantly lower than that in normal tissues, and the immunohistochemistry results also suggested that the expression level of Cavin3 protein was lower than that in normal samples.However, there is currently no independent research on the mechanism of action of Cavin3 in cervical cancer, and its specific biological functions still need to be further explored.

Outlook

As an important cell membrane protein, Cavin3 plays a key role in various malignant tumors. Current studies have shown that Cavin3 is generally downregulated in a variety of malignant tumors such as breast cancer, lung cancer, gastric cancer, colorectal cancer, and gynecological tumors, and this downregulation is closely related to the hypermethylation of its promoter region. In terms of molecular mechanism, Cavin3 is not only involved in the formation and stabilization of caveolae, but also plays a tumor suppressor role by regulating multiple key signaling pathways. In breast cancer, Cavin3 participates in DNA damage repair by inhibiting the PI3K/AKT signaling pathway and interacting with BRCA1; in lung cancer, Cavin3 is associated with the p53 pathway and ROR1-caveolar-dependent endocytosis; in gastric cancer, it mainly induces cell cycle arrest and apoptosis by stabilizing p53 and activating the p21Waf1/PUMA/NOXA pathway; in colorectal cancer, Cavin3 acts as an oncogene mainly through epigenetic alterations (eg CpG island methylation-associated silencing), and its expression level is strongly correlated with the resistance of cancer cells to oxaliplatin. These findings fully demonstrate that Cavin3 may exert tumor suppressor effects through different molecular mechanisms in different tumor microenvironments.

Although significant progress has been made in the study of Cavin3 in tumors, it still faces the following problems and challenges. First, the understanding of the molecular mechanism of action of Cavin3 is still not deep enough. Although it is known to be involved in regulating multiple signaling pathways, the precise molecular mechanisms of how it interacts with these pathways remain unclear, especially the differences in regulation under different tumor microenvironments. Secondly, the differential effects of Cavin3 in different tumors have not been fully explained. Currently, there is a lack of a systematic explanation for why Cavin3 exhibits different or even opposite functions in different tumor types, which is also the main obstacle limiting its application as a universal tumor marker. Finally, the clinical translation and application of Cavin3 research results face challenges. Although Cavin3 has promise as a potential biomarker and therapeutic target, specific detection methods and targeted treatment strategies for Cavin3 are still in their early stages, and clinical applications still face many obstacles.

Based on the existing research foundation and existing problems, the precise interaction mechanism between Cavin3 and tumor-related signaling pathways should be further explored in the future, especially the differences in its regulatory network in different tumor microenvironments. In terms of drug target development, we can focus on exploring epigenetic drugs that restore Cavin3 expression, or small molecule inhibitors targeting its downstream effector molecules. For instance, demethylating drugs targeting Cavin3 promoter methylation, or inhibitors targeting the ROR1-Cavin3 complex, may provide new strategies for precision tumor treatment. In the application of personalized precision

medicine, there is an urgent need to develop a highly sensitive and specific Cavin3 detection method and explore its combined application with other molecular markers to improve the accuracy of early tumor diagnosis and prognosis assessment. For example, in colorectal cancer, Cavin3 methylation status may become a biomarker for predicting oxaliplatin sensitivity, providing a basis for individualized treatment decisions.

In summary, Cavin3, as an important tumor suppressor molecule, plays a complex and critical regulatory role in the occurrence and development of various malignant tumors. In-depth research on its molecular mechanism and clinical application value will not only help reveal new mechanisms of tumor occurrence and development, but also provide new molecular targets for early diagnosis and precision treatment of tumors, which has important scientific significance and clinical application prospects.

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Disclosure

The authors report no conflicts of interest in this work.

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