Myosin Heavy Chain 9: Oncogene or Tumor Suppressor Gene?

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MYH9 was first discovered due to thrombocytopenia caused by *MYH9* mutation-related abnormalities. In recent years, researchers have increasingly found that *MYH9* plays an important role in cancer as a cytokine involved in cytoskeletal reorganization, cellular pseudopodia formation, and migration. *MYH9* is closely related to the progress and poor prognosis of most solid tumors, and it is now accepted that MYH9 is a suppressor gene and plays an important role on the re-Rho pathway. Recent research has been limited to the study of tissues. However, it would be more direct and informative to be able to use hematology to assess tumor prognosis and changes in MYH9 levels and NMMHC-IIA. This article summarizes recent research on *MYH9 and* provides a reference for future clinical research.

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Background

Myosin heavy chain 9 (MYH9) encodes a protein called non-muscle myosin II (NMM-II), which belongs to the myosin superfamily. NMM-II is a hexamer composed of 2 heavy chains (220 kDa), 2 regulatory light chains (RLC, 20 kDa), and 2 essential light chains (ELC, 17 kDa). There are 3 types of hexamers – IIA, IIB, and IIC – that are encoded by MYH9, MYH10, and MYH14, respectively, located on chromosomes 22, 17, and 19, respectively. The structure of NMMHC-IIA consists of 3 parts: an N-terminal polar head, a neck, and a C-terminal non-polar tail. The N-terminal head is the functional area, which has ATPase activity, including ATP and actin binding sites; the neck can bind to the light chain and balances regulation; and the C-terminal tail is a rod-like helix dimer that can polymerize molecules into bipolar polythene. Non-muscle myosin IIA (NMM-IIA) plays an important role in cell adhesion, migration, proliferation, and differentiation. The present review focused on research on MYH9 as a tumor suppressor gene and on the relationship between MYH9 and RhoA. Finally, the correlation between MYH9 and clinical manifestations (solid tumors and hematological tumors) is discussed.

MYH9-Related Thrombocytopenia

MYH9 was first discovered due to thrombocytopenia caused by *MYH9* mutation-related abnormalities, such as May-Hegglin anomaly (MHA), Epstein syndrome (EPS), Fechtner syndrome (FTNS), and Sebastian syndrome (SBS), which are autosomal dominant genetic diseases [1,2]. Laboratory examination of these diseases shows thrombocytopenia and giant platelet and neutrophil cytoplasmic inclusion bodies. Because *MYH9* is expressed in the kidneys, retinas, and ears, patients usually have neurological deafness, premature cataracts, and glomeruli nephritis after age 50 years. Laboratory diagnosis mainly depends on morphological indicators (cell volume), a peripheral blood smear (neutrophil cytoplasmic inclusive), immunofluorescence (NMM-IIA inclusive), gene mutation analysis (*MYH9* has 40 known exonic mutations, which help assess the patient's risk of renal/retinal and ear pathology), and flow cytometry (detection of platelet glycoproteins such as GPIb and CPIX contribute to the differential diagnosis) [3]. Therefore, clinically indefinable thrombocytopenia should first exclude myelodysplastic syndromes (MDS), aplastic anemia, idiopathic thrombocytopenic purpura (ITP), Alport syndrome, and other diseases. If there are clear genetic factors, MYH abnormal thrombocytopenia should be further validated, such as MHA, EPS, FTNS, and SBS. Many genetic studies have been performed on MYH9-related diseases. Using high-throughput sequencing (HTS), Noris et al. [4] found that 33 genetic diseases were caused by 32 gene defects, clearly explaining the pathogenesis of these diseases. In a gene mutation test,

Anna et al. [5] found a relationship between more than 80 genetic mutations, specific mutations, and features of clinical diseases; mutations affecting residue R702 (exon 17) are correlated with severe thrombocytopenia, end-stage renal disease, and early episodes of deafness. Mutations in exon 2, mutations affecting residues R1165 (exon 26), and a p.D1424H substitution (exon 31) are associated with moderate risk of thrombocytopenia and additional hematologic manifestations. Finally, mutations affecting the C-terminal non-helical tail, p.D1424N (exon 31), p.E1841K (exon 39,) or nonsense/frameshift mutations are associated with moderate thrombocytopenia and extravasation manifestations.

MYH9 in Chemotherapy

In recent years, researchers have increasingly found that *MYH9* plays an important role in cancer as a cytokine involved in cytoskeletal reorganization, cellular pseudopodia formation [6,7], and migration [8]. It is a critical factor for tumor invasion and metastasis, which has been confirmed in many studies [9]. High expression of *MYH9* is usually found in non-small cell lung cancer, breast cancer, leukemia, gastric cancer, esophageal cancer, and other malignant tumors. *In vivo* studies found that up-regulation of *MYH9* expression can increase the sensitivity of leukemia cytotoxicity, resulting in chemoresistance. Acute myeloid leukemia (AML) patients with high expression of *MYH9* have clear microRNA (miRNA) markers [10]. Previous studies have found that down-regulation of 18 miRNAs and up-regulation of 3 miRNAs resulted in increased *MYH9* expression, and an association was found between low MIR-188-5p and overall survival (OS) and event-free survival (EFS) of cytogenetically normal acute myeloid leukemia CN-AML. mi-16-1 is often used as an indicator of the prognosis of chronic myeloid leukemia and miR-29c can be used as a predictor of prognosis and response in AML patients with cytarabine. *MYH9* overexpression is also related to M4 (acute myeloblastic leukemia). Patients with M4 and high expression of *MYH9* are prone to invasion of skin, bone marrow, and other tissues, and are resistant to chemotherapy. In AML, *MYH9* can be used as a prognostic indicator, as clinical observations found that AML patients with high expression have poor prognosis. In multivariate analysis, OS [hazard ratio (HR) (95% confidence interval (CI), 1.69 (1.17, 2.43); *P*=0.005,], and there was a statistically significant difference between high expression and normal expression.

Relationship Between MYH9 and Tumor Staging

MYH9 is closely related to the progression and poor prognosis of gastric cancer and esophageal cancer, suggesting a potential role in promoting cancer. Previous studies have shown that

high expression of the *MYH9*-encoded protein NMIIA is associated with poor prognosis in multiple regression analysis. *MYH9* is significantly and positively correlated with gastric cancer invasion depth, lymph node metastasis, distant metastasis, and node-metastasis (TNM) staging [13]. *MYH9* overexpression can cause invasion and metastasis of gastric cancer cells [14]. Schramek [15] proposed that *MYH9* could be used as an indicator to observe the progression and prognosis of gastric cancer. The expression of *MYH9* in esophageal cancer tissues was 100%, while the expression in adjacent tissues was 50%. Multi-factor regression analysis showed that *MYH9* expression was correlated with lymph node metastasis (*P*=0.015, differentiation (*P*=0.018) and the progression of tumor staging (stage IIIB and IIIC, *P*=0.007<0.01) [16]. *MYH9* was highly expressed in most colorectal cancer patients. The positive rates of MYH9 protein in colorectal adenocarcinoma tissues and paracancerous tissues were 51.6% and 11.5%, respectively. *MYH9* expression in colorectal cancer [17] is significantly associated with patient age, clinical stage, lymph node metastasis, and metastasis distance. Survival analysis using Kaplan-Meier method showed that the high expression of *MYH9* in primary tumors was significantly associated with shortened survival. Five-year cumulative survival rates were 49% (31/63) and 86% (51/59) in patients with high and low expression of *MYH9*, respectively. The median survival period was 65.4 months (95%CI=54.8–76.0) and 95.1 months (95% CI=84.9–105.4), respectively, and this difference was statistically significant (P<0.001). Additionally, multivariate analysis showed that *MYH9* overexpression was an independent prognostic factor in patients with colorectal adenocarcinoma. miRNA (miRNA124) was found to silence *MYH9* expression and inhibit invasion and metastasis by binding to the *MYH9* 3'-untranslated region (UTR). Liao et al. [18] identified 2 tumor metastasis-associated proteins – MYH9 and ACTN4 – that are required for LIMK1-mediated aggressive phenotypes. Also, LIMK1 was aberrantly regulated in various types of human cancers and contributed to cancer progression. Another study found that MYH9 down-regulated many small interfering RNAs (siRNAs) in pancreatic cancer patients, and the down-regulation of tumor suppressor genes led to the occurrence of tumors [19]. Non-small cell lung cancer studies showed that the expression of *MYH9* was up to 38.3%; *MYH9* was not detected in small cell lung cancer cells, but multivariate analysis showed that *MYH9* expression was correlated with poorly differentiated tumors, vascular invasion, and lymph node invasion. Therefore, *MYH9* is an independent prognostic factor for lung cancer (in patients with stage 1–3 resectable non-small cell lung cancer); furthermore, it has been found that patients with resectable non-small cell lung cancer and patients with high expression of *MYH9* had poor prognoses. Another study showed that the lack of *MYH9* or vimentin expression in stage 1 non-small cell lung cancer led to good prognosis after adjuvant chemotherapy. *MYH9* in osteosarcoma cells has been shown to be highly expressed

(75.38% of total immunohistochemical markers) and clinical data show that positive expression is associated with Enneking staging and lung metastases but is not correlated with age, sex, or tumor diameter. MYH9 overexpression can promote tumor invasion and metastasis, and the mechanism of tumor promotion and metastasis is putatively related to the epithelial-mesenchymal transition (EMT), which has been confirmed in breast cancer cells [21].

MYH9 as a Tumor Suppressor Gene

In skin cancer and in head and neck squamous cell carcinomas, NMIIA has been found to be a tumor suppressor protein [15]. *In vivo* experiments show that tumor cell metastasis is promoted after skin cancer cells inhibit NMIIA, and the incubation period is about 2–3 months. Additionally, it was also found that low expression of NMIIA was related to poor prognosis of patients with squamous cell carcinoma of the head and neck, which may be related to mutations in *MYH9*. Mutations in *MYH9* were found in about 5% of patients, with these mutations mainly occurring in the NMIIA MgATP domain or the entire NMIIA molecule, and these mutations may be MYH9-related diseases or may eventually develop into skin cancer [22]. Wei et al. [23] showed that as a target of anti-tumor metastasis, DT13 reversed hypoxic effects by up-regulating the expression of NMIIA in a hypoxic environment; furthermore, NMIIA was redistributed to the nucleus and inhibited the metastasis of 95D cells (a lung cancer cell line) by suppressing the formation of actin F. It has been found [24] that MYH9 binds to the promoter region of long-chain non-coding RNA (lncRNA) in thyroid cancer tissues and cells and acts as a suppressor of *PTCSC2* and bi-directionally actives *FOXE1* promoter regions. MYH9 plays a role in the P53 pathway through FOXE1; MYH9 affects *PAX5* expression through its interaction with Thy28 (thymocyte protein) [25] and activates AKT (protein kinase B) through *RAC1* and *PAK1* [26], suggesting its role in gene regulation. Furthermore, NMIIA is closely related to post-transcriptional stability and nuclear retention of p53 [27] in this process, and the NMIIA MgATP enzyme plays a major role; for tumor phenotypes, the NMIIA protein mainly rely mainly on tumor suppressor protein (Lgl1) to play a role. However, if Lgl1 is phosphorylated, binding is prevented [26]. P53 is stable after transcription, but its underlying mechanism is unclear. Lamet et al. [28] found that more than 20 ALK fusion partners have been identified in various cancers since the discovery of nuclear phosphoprotein-anaplastic lymphoma kinase (NPM-ALK), including the t(2.22) (p23, q11.2) translocation in the MYH9-ALK chimera. It is interesting that, unlike other *ALK* chimeras, *MYH9-ALK* lacks an oligomerization domain and thereby lacks tyrosine kinase activity. *In vitro* tyrosine residues are phosphorylated *in vivo* via mechanisms that may differ from other *ALK* hybrids.
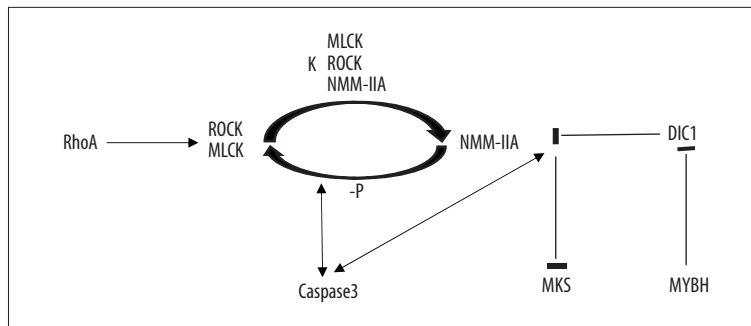
Figure 1. The mechanism diagram with the MYH9 and Rho pathway. RhoA – Ras homolog gene family, member A; NM IIA – non-muscle myosin IIA; MLCK – myosin light chain kinase; ROCK – Rho-associated, coiled-coil-containing protein kinase; MYBH – myosin-binding protein H; MKS – megakaryocytes.

MYH9 and the Rho Pathway

It has been shown that non-myosin II plays an important role in many functions, such as cell migration, cytokinesis, cell adhesion, cell morphology, cell polarity, and cell tropism [28,29]. Tumor research has shown that many of these functions are involved in malignant transformation, invasion, and metastasis. MYH9 can be localized in the cell membrane and cytoplasm in some tumor cells. Additionally, in MDA-MB-231 (a breast cancer cell line), the lamellar form of MYH9 was observed to diffuse into fibronectin within cells, which was related to the invasion and metastasis of the tumor cells. Meanwhile, in a comparison between MCF7 cells (high expression of *MYH9*) and MCF6/7 cells (low expression of *MYH9*), we observed that the former had stronger invasive ability, and its invasion ability was clearly weakened after knockout of *MYH9*. The function of MYH9 [30] depends mainly on the Rho GTPase family (small G proteins). So far, 23 signaling molecules are known in this family, and studies have shown that RhoA, Rac1, cdc42, and RhoA induce contractile actin to assemble and build microfilaments. Rac regulates the formation of layered footplates and membrane fold-like movement. Activation of Cdc42 is necessary for the formation of silk footprints. Studies have shown that the myosin IIA-actin complex contributes to myosin contractility and is associated with a positive feedback loop of the caspase-3/ROCK1/MLC (Rho-associated kinases/myosin light chain) pathway [31].

NM IIA can be activated by phosphorylation of the 20 kDa light chain on serine 19 (S-19) and threonine 18 (T-18), most notably (MLCK) and 20 kDa-regulated light chain Rho kinase phosphorylation-induced bipolar filament [32–34]. Formation significantly increased actin-activated Mg ATPase activity and allowed myosin silk to slide myosin [35,36]. Protein phosphatase 1 dephosphorylates these sites *in vivo*. Notably, this phosphatase activity can be reduced by phosphorylation of its Rho kinase-mediated regulatory subunit. Rho kinase phosphorylation increases NMIIA activity by phosphorylating NMIIA to regulate light chain inactivation and phosphatase dephosphorylates the light chain. Myosin-binding protein H (MYBH) has been reported to inhibit NMIIA phosphorylation on the light chain by direct interaction with Rho kinase 1 in the lung. In addition, it is shown that MYBH can also inhibit myosin assembly

by directly interacting with the rod portion [37]. NMIIA thus reduces cell motility and reduces lung metastasis. In another report [38], MYBH was found to attenuate neointimal hyperplasia in a rat model of carotid injury by inhibiting Rho kinase 1, and Dlc1 may be involved in the reduction of MYH9 fiber stability and interacts with phosphorylated MYH9 (Ser-1943). Dlc1 also inhibits stress fiber formation via Rho and phosphorylation of MYH9-activated ROCK kinase via MLC20 [39]. The transcription co-activator p300 is highly expressed in breast cancer tissues. MRTF-A is a transcription factor controlled by the Rho-GTPase-actin signaling pathway. P300 synergizes with MRTF-A to activate MYH9-mediated gene regulation and breast cancer cell migration [40].

MLC phosphorylation in MKs (megakaryocytes) is regulated by Rho-associated kinase (ROCK), and ROCK inhibition enhances proplatelet formation (PPF). In contrast, expression of AV14 (a constitutive form of ROCK activator Rho) blocks PPF and this effect is rescued by the inhibitory MLC form. The Rho-ROCK-myosin-IIA pathway selectively reduces the number of circulating platelets [41]. The following is the mechanism diagram of the MYH9 and Rho pathway (Figure 1).

Conclusions

Whether *MYH9* is an oncogene or a tumor suppressor gene is still unclear. In previous studies, *MYH9* has been shown to encode a tumor suppressor protein in head and neck tumors and skin tumors, but acts as an oncogene in other solid and hematological tumors. *MYH9* research has now been performed in many solid tumor types, in mesenchymal tumors, and in hematological diseases. In general, *MYH9* and its encoded protein are related to poor prognosis, lymph node metastasis, tumor progression, and tumor differentiation. However, recent research has been limited to the study of tissues, and *MYH9* cannot be used clinically as an indicator of dynamic changes in tumor prognosis. If the changes in NMMHC-IIA could be determined by hematology, the assessment of tumor prognosis and changes in MYH9 levels would be more direct and informative. This article summarizes recent research on *MYH9* and provides a reference for future clinical research.

Acknowledgments

Conflicts of interest

None.

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