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Review Article

Progress of dynamin 3 in tumors

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Abstract: Dynamin 3 comes from an ancient family of GTPase, who encodes 3 classical genes but share the basic structure composing of different domains. Every domain has its special binding partner and shows different features respectively. Current evidence has shown that dynamin 3 is deregulated in various diseases, including sarcoma, Sezary syndrome, hepatocellular carcinoma and colorectal cancer. On the basis of the above, we predict that dynamin 3 may be a novel candidate of tumor suppressor genes. Here, we review the research progress of dynamin 3 expression of human diseases and discuss the probable mechanism of dynamin 3 in tumors growth and progression.

Keywords: Dynamin 3 (dynamin-3, DNM 3), dynamin, tumor, tumor suppressor genes, P53

Introduction

Normal cells become malignant largely as a result of multiple genetic lesions that activate tumor genes and inactivate suppressor tumor genes. As the Molecular Genetics developed, about 50 oncogenes and a dozen anti-oncogenes have been cloned and sequenced [1]. The functions and mechanism in tumorigenesis of some of them have been clearly understood, and some of them even used for therapy. However, complete understanding of tumorigenic requires additional information since its polygenic. More and more scholars are committed to discover new tumor-suppressor genes and find out the drugs to active them so that brings benefit to the cancer patients. Dynamin 3, which comes from a huge family, is a gene found to be related to tumors in recent years.

Dynamin was first isolated from bovine brain in 1989s and identified as microtubule-associated motors [2]. From then on, our understanding of dynamins has expanded significantly. Dynamins are known as a 100-kDa GTPase, which encode 3 genes, dynamin 1, 2, 3, differ particularly within their C-terminal region sharing the same basic structure: an N-terminal GTPase domain (G domain) that control GTP hydrolysis, a middle domain (stalk domain) mediates the dynamin oligomerization along with the GTPase effector domain (GED) form a "stalk" structurally, a pleckstrin-homology (PH) domain that binds inositol phospholipids, a domain with a propensity to form coiled coils (the assembly domain, also named the GTPase effector domain or GED) and a C-terminal proline-rich domain (PRD) that allows interaction with SH3-domain-containing-proteins [3-10] (**Figure 1**). The remarkable property happens to the ability to self-assemble into complex polymers, which constrict when GTP is hydrolyzed. In the exploration process of dynamins, they found that dynamins have a close relationship with a series of cell activities.

According to the lately survey, dynamin 3 is low-expressed in tumor tissue samples and cell lines of human cancers. We review a large number of literatures, and carry out an attempt on discussion about the underlying mechanism.

Expression of dynamin 3 in various diseases (Table 1)

Booken N [11] confirmed that dynamin 3 is upregulated in the peripheral blood mononuclear cells (PBMC) of Sezary syndrome (SS)

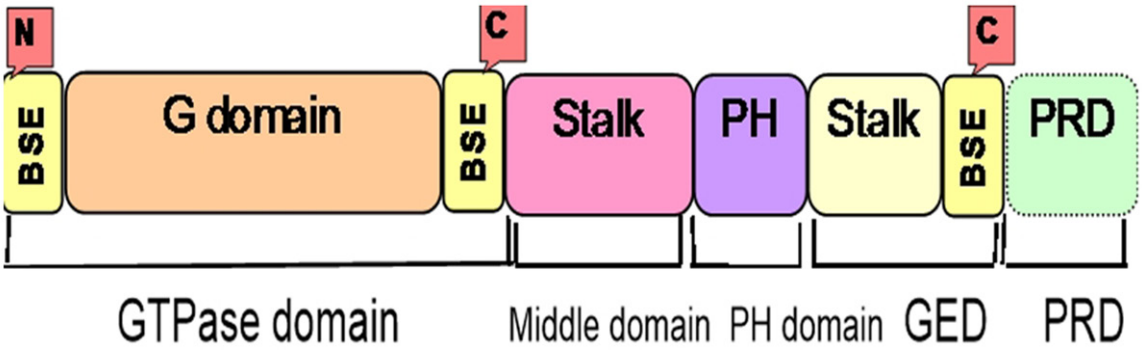

Figure 1. Basic structure of dynamin family members. BSE: bundle-signaling element, middle domain: stalk domain, PH: pleckstrin-homology domain, GED: GTPase effector domain, PRD: proline-rich domain.

Table 1. Expression status of dynamin 3 in various diseases

Author	Year	Diseases	Expression of dynamin 3
Booken N [11]	2008	Sezary syndrome	Up-regulated
Teicher B [12]	2012	Liposarcomas	-
Shen J [13]	2012	Hepatocellular carcinoma	Down-regulated
Inokawa Y [14]	2013	Hepatocellular carcinoma	Down-regulated
Zhang Z [15]	2016	Hepatocellular carcinoma	Down-regulated

through comparing 10 SS patients and 10 healthy donors (HD) using Affymetrix U133 Plus 2.0 chips and quantitative realtime polymerase chain reaction (qRT-PCR). They also found that the expression level of dynamin 3 was regulated by SS-associated transcription factors TWIST1 and c-myb, suggesting a possible role in the process of T-cell lymphoma.

Teicher B [12] found 1q 24.3 amplifications involving dynamin 3 in 33% well-differentiated and 35% de-differentiated sarcomas. However, the deeper research about the relationship between the expression of dynamin 3 and sarcomas has not been conducted.

A survey from Shen J [13] firstly identified dynamin 3 as one of gene methylated in tumor tissues compared to adjacent normal tissues from 62 Taiwanese hepatocellular carcinomas (HCC) cases using Illumina methylation arrays. However, the expression status of dynamin 3 was not studied in their survey. Subsequently, Inokawa Y [14] put forward that dynamin 3 was a tumor suppressor gene in hepatocellular carcinomas (HCC) since dynamin 3 was down regulated obviously in hepatocellular carcinomas (HCC) by triple combination array analysis. They also found that methylation of dynamin 3 reduced its gene expression and was concerned with a worse prognosis. Zhang Z [15] conducted a study to verify the loss of dynamin 3 expressions in hepatocellular carcinomas (HCC) tissues and cell lines, and discovered the close relationship of dynamin 3 with vein invasion and tumor metastasis. As showed in the article, dynamin 3 restrains proliferations and colony formation of hepatocellular carcinoma (HCC) cells when increased via quantitative realtime polymerase chain reaction (qRT-PCR) and Western blot analysis. Furthermore, flow cytometry confirmed that dynamin 3 can induce G0/G1 cell cycle arrest and promote hepatocellular carcinoma cell apoptosis. So far, we have a deeper understanding about influence on hepatocellular carcinomas by the expression status of dynamin 3. Nevertheless, the mechanism underlying the anti-proliferative effect of dynamin 3 remains unknown.

Additionally, a new research about the relationship between dynamin 3 and colorectal cancer is ongoing in our team-members. By collecting surgical specimens and pathological sections, we have found a vital clue that dynamin 3 is positively expressed in the adjacent normal tissue and negative expressed in colorectal cancer tissue on the contrary (**Figure 2A**, **2B**). More experiments on cell lines are still performing. The association between dynamin 3 and clinical pathologic characteristics is under investigated.

Taken together, we put forward a viewpoint that dynamin 3 may be a novel candidate of tumor

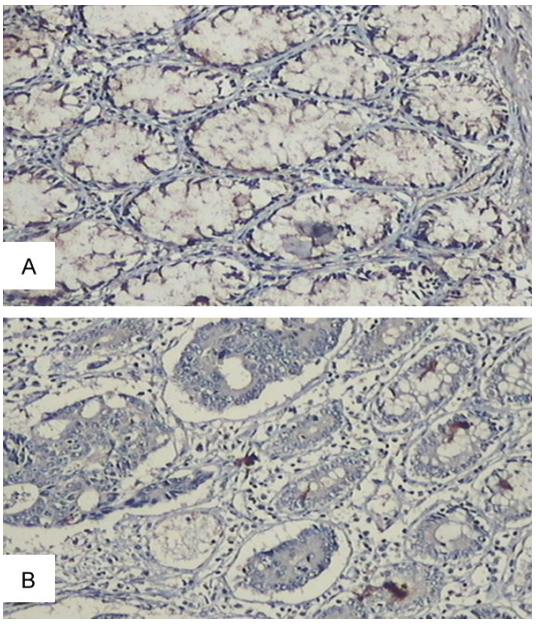

Figure 2. The expression status of dynamin 3 in colorectal cancer. (A) Positive expressed in the adjacent normal tissue and (B) negative expressed in the tumor tissue (Hematoxylin staining method, Micrographs were taken at an original magnification of x200).

suppressor gene. However, reviewing a large number of the latest articles, there is still no exact theory to illustrate the underlying mechanism.

Tumor suppressor genes often have a role in inhibiting cell proliferation and tumor generation with cancer gene antagonism. And their missing or mutation results in the rapid cell proliferation which leads to the process of carcinogenesis. The relationship between deactivation or lack of dynamin 3 and tumor cells proliferative potential remains unknown. Deeper researches are demanded.

Inokawa Y [14] consider that the low expression of methylated dynamin 3 plays its role in tumor invasion and metastasis via upregulating MMP2, a type IV collagenase [16], whose proteolytic fragments directly blocked the tumor angiogenesis of various carcinomas, including hepatocellular carcinoma (HCC) [17]. Zhang Z [15] took p53 into consideration just because p53 was over-expressed in cultured dynamin 3 cell lines through western blot analysis. Cao S [18] have demonstrated that binding the proline-rich domain (PRD) of dynamin 2 and the FAD-binding region of the endothelial nitric-oxide synthase (eNOS) reductase domain can invoke eNOS and raise NO production. And p53 induce cell cycle arrest and promotes hepatocellular carcinoma cell apoptosis when activated by NOS. Until now, it is the most convincing standpoint about how dynamin 3 functioned in the cancers as a tumor suppressor gene.

P53, known as a multifunctional transcription, transactivates a variety of genes implicated in programmed necrosis, cell cycle progression, cell death signaling, metabolism, DNA repair, and angiogenesis [19]. It is one of the most popular tumor suppressor genes, and has been found in numerous cancers. In addition, p53 has huge potential value for treatment, diagnosis and prognosis, so that quite a few researches about signaling pathway in p53 have been made. Once activated, p53 binds to a unique DNA sequence, term the p53-responsive element, and regulate their expression in its target genes [20]. Besides, mutant p53 can gain new oncogenic functions instead of losing their tumor suppression and inhibit the function of wild-type p53 through the dominant negative effect [21]. JI L also showed an interesting mechanism that mutant p53 protein gains multiple new activities contributing to tumorigenesis by attenuating and cooperating with the TGF-β pathway via targeting Smad 3 [22-23]. Certainly, further studies on p53 will be required urgently to lead to the development of cancer-specific p53-based therapy and novel chemicals to markedly improve cancer therapy.

Conclusion

In conclusion, dynamin 3 might be a novel candidate of tumor suppressor gene. It was deregulated in different diseases including Sezary syndrome (SS), liposarcomas, hepatocellular carcinoma (HCC) and colorectal cancer, and also associated clinical features. Nowadays, genetic therapy for tumor patients has become a hotspot. Dynamin 3 is supposed to be one of target genes, even a biological marker, therapeutic tragedy after further researches.

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Disclosure of conflict of interest

None.

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References

[1] Bouck N. Angiogenesis: a mechanism by which oncogenes and tumor suppressor genes regulate tumorigenesis. Cancer Treat Res 1992; 63: 359-371.

[2] Urrutia R, Henley JR, Cook T and McNiven MA. The dynamins: redundant or distinct functions for an expanding family of related GTPases? Proc Natl Acad Sci U S A 1997; 94: 377-384.

[3] Tanifuji S, Funakoshi-Tago M, Ueda F, Kasahara T and Mochida S. Dynamin isoforms decode action potential firing for synaptic vesicle recycling. J Biol Chem 2013; 288: 19050-19059.

[4] van der Bliek AM. Functional diversity in the dynamin family. Trends Cell Biol 1999; 9: 96-102.

[5] Gonzalez-Jamett AM, Momboisse F, Haro-Acuna V, Bevilacqua JA, Caviedes P and Cardenas AM. Dynamin-2 function and dysfunction along the secretory pathway. Front Endocrinol (Lausanne) 2013; 4: 126.

[6] Cao H, Garcia F and McNiven MA. Differential distribution of dynamin isoforms in mammalian cells. Mol Biol Cell 1998; 9: 2595-2609.

[7] Reubold TF, Faelber K, Plattner N, Posor Y, Ketel K, Curth U, Schlegel J, Anand R, Manstein DJ, Noe F, Haucke V, Daumke O and Eschenburg S. Crystal structure of the dynamin tetramer. Nature 2015; 525: 404-408.

[8] Kruchten AE and McNiven MA. Dynamin as a mover and pincher during cell migration and invasion. J Cell Sci 2006; 119: 1683-1690.

[9] Mettlen M, Pucadyil T, Ramachandran R and Schmid SL. Dissecting dynamin's role in clathrin-mediated endocytosis. Biochem Soc Trans 2009; 37: 1022-1026.

[10] Antonny B, Burd C, De Camilli P, Chen E, Daumke O, Faelber K, Ford M, Frolov VA, Frost A, Hinshaw JE, Kirchhausen T, Kozlov MM, Lenz M, Low HH, McMahon H, Merrifield C, Pollard TD, Robinson PJ, Roux A and Schmid S. Membrane fission by dynamin: what we know and what we need to know. EMBO J 2016; 35: 2270-2284.

[11] Booken N, Gratchev A, Utikal J, Weiss C, Yu X, Qadoumi M, Schmuth M, Sepp N, Nashan D, Rass K, Tuting T, Assaf C, Dippel E, Stadler R, Klemke CD and Goerdt S. Sezary syndrome is a unique cutaneous T-cell lymphoma as identified by an expanded gene signature including diagnostic marker molecules CD01 and DNM3. Leukemia 2008; 22: 393-399.

[12] Teicher B. Searching for molecular targets in sarcoma. Biochem Pharmacol 2012; 84: 1-10.

[13] Shen J, Wang S, Zhang YJ, Kappil M, Wu HC, Kibriya MG, Wang Q, Jasmine F, Ahsan H, Lee PH, Yu MW, Chen CJ and Santella RM. Genome-wide DNA methylation profiles in hepatocellular carcinoma. Hepatology 2012; 55: 1799-1808.

[14] Inokawa Y, Nomoto S, Hishida M, Hayashi M, Kanda M, Nishikawa Y, Takeda S, Fujiwara M, Koike M, Sugimoto H, Fujii T, Nakayama G, Yamada S, Tanaka C, Kobayashi D and Kodera Y. Dynamin 3: a new candidate tumor suppressor gene in hepatocellular carcinoma detected by triple combination array analysis. Onco Targets Ther 2013; 6: 1417-1424.

[15] Zhang Z, Chen C, Guo W, Zheng S, Sun Z and Geng X. DNM3 attenuates hepatocellular carcinoma growth by activating P53. Med Sci Monit 2016; 22: 197-205.

[16] Devarajan P, Johnston JJ, Ginsberg SS, Van Wart HE and Berliner N. Structure and expression of neutrophil gelatinase cDNA. Identity with type IV collagenase from HT1080 cells. J Biol Chem 1992; 267: 25228-25232.

[17] Egeblad M and Werb Z. New functions for the matrix metalloproteinases in cancer progression. Nat Rev Cancer 2002; 2: 161-174.

[18] Cao S, Yao J and Shah V. The proline-rich domain of dynamin-2 is responsible for dynamin-dependent in vitro potentiation of endothelial nitric-oxide synthase activity via selective effects on reductase domain function. J Biol Chem 2003; 278: 5894-5901.

[19] Stegh AH. Targeting the p53 signaling pathway in cancer therapy-the promises, challenges and perils. Expert Opin Ther Targets 2012; 16: 67-83.

[20] Liu J, Zhang C and Feng Z. Tumor suppressor p53 and its gain-of-function mutants in cancer. Acta Biochim Biophys Sin (shanghai) 2014; 46: 170-179.

[21] Ji L, Xu J, Liu J, Amjad A and Zhang K. Mutant p53 promotes tumor cell malignancy by both positive and negative regulation of the transforming growth factor β (TGF-β) pathway. J Biol Chem 2015; 290: 11729-11740.

[22] Sigal A and Rotter V. Oncogenic mutations of the p53 tumor suppressor: the demons of the guardian of the genome. Cancer Res 2000; 60: 6788-6793.

[23] Kim E and Deppert W. Transcriptional activities of mutant p53: when mutations are more than a loss. J Cell Biochem 2004; 93: 878-886.