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Dynamins and BAR Proteins—Safeguards against Cancer

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Abstract

Dynamins and BAR proteins are crucial in a wide variety of cellular processes for their ability to mediate membrane remodeling, such as membrane curvature and membrane fission and fusion. In this review, we highlight dynamins and BAR proteins and the cellular mechanisms that are involved in the initiation and progression of cancer. We specifically discuss the roles of these proteins in endocytosis, endo-lysosomal trafficking, autophagy, and apoptosis as these processes are all tightly linked to membrane remodeling and cancer.

Keywords

cancer; dynamin; endophilin; Drp1; Mfn; Opa; BAR domain; membrane fission and fusion

I. Introduction

Dynamins and members of the BAR protein family (“BAR proteins”) mediate membrane remodeling during fundamental cellular processes, such as synaptic vesicle recycling, mitochondrial fragmentation, ER fusion, and downregulation of cell surface receptors.^{1–3} Dynamins are atypical GTPases broadly implicated in membrane fission and fusion events in the cell.^{1,3} Dynamin, the founding member of this superfamily, is crucial for endocytosis, synaptic membrane recycling, and membrane trafficking within the cell.⁴ Dynamin assembles into polymers on the necks of budding membranes in cells and has been shown to undergo GTP-dependent conformational changes that lead to membrane fission *in vitro*.^{5–10} This led to the model that dynamin pinches off vesicles by wrapping around and constricting the necks of budding vesicles.^{11,12} Additional dynamin family members have been implicated in a variety of fundamental cellular processes, including mitochondrial fission and fusion, antiviral activity, plant cell plate formation, and chloroplast biogenesis.^{1,3,13,14} Among these proteins, self-assembly, oligomerization into ordered structures, and GTPase activity are common characteristics and, for the majority, essential for their functions.

BAR proteins are major contributors to membrane remodeling events in the cell. They are also involved in the regulation of the actin network, cell migration, T-tubule formation, cell motility, and neuromorphogenesis. Depending on the shape of the BAR domain dimer, BAR

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proteins sense and induce either positive (N- and F(FCH)-BAR proteins)^{15–20} or negative curvature [(inverse)-BAR proteins].^{21–23} BAR domains bind the membrane via electrostatic interactions with lipid head groups. N-BAR proteins contain an amphipathic helix in their N-terminus (hence the name N-BAR), which inserts into the lipid bilayer and may play a role in curvature sensing.^{17,24} N-BAR proteins, like endophilin and amphiphysin, promote high curvatures, like the highly constricted necks of clathrin-coated pits^{15,17,19,20} while F-BAR proteins, like syndapin, CIP4 and FBP17, have been shown to stabilize more shallow membrane deformations.^{16,18,25}

II. Endocytosis and intracellular signaling

Endocytic internalization and endo-lysosomal trafficking of cell-surface receptors, like EGFR and VEGFR, are crucial events in the intracellular signaling pathways that regulate cell growth and proliferation. If interrupted, these may lead to carcinogenesis, which is why proteins controlling these pathways are of great interest in the effort to elucidate the molecular mechanisms of cancer pathogenesis and identify novel modes of prevention.

Evidence is emerging that expression of the ubiquitous isoform of dynamin, dynamin 2, may provide a useful tool for the prognosis of some cancers.²⁶ One prospective role of dynamin in cancer cells is downregulation of receptors like EGFR at the plasma membrane through clathrin-mediated endocytosis.²⁷ Several groups have associated increased levels of EGFR with cancer cell growth.^{26–28} Internalization and subsequent downregulation of EGFR leads to decreased phosphorylation of ERK.^{29,30} Phosphorylation of ERK is generally associated with uncontrolled cell growth in numerous cancers.³¹ Hence, one possible pathway to regulate ERK phosphorylation is through dynamin 2-dependent internalization of EGFR. Therefore, dynamin 2 may play a role in carcinogenesis by controlling cell signaling pathways involved in cell growth and proliferation. It has also been shown that in cervical cancer cells, low levels of dynamin 2 correlate with an increase in matrix metalloproteinase-2 expression, which leads to greater tumor invasion.³² Thus, expression of dynamin 2 may lead to downregulation of matrix metalloproteinase-2, though how this occurs is not yet clear. Overall, the correlation between low levels of dynamin 2 and increased tumorigenesis is likely due to defects in membrane fission.

Dynamin interacts with a number of accessory proteins during clathrin-mediated endocytosis and intracellular membrane trafficking. Major binding partners of dynamin are endophilin, amphiphysin, syndapin (also referred to as pacsin), Cdc42 interacting protein 4 (CIP4), and forming-binding protein 17 (FBP17).² BAR proteins facilitate dynamin-mediated plasma membrane fission during endocytosis, possibly by generating optimal membrane curvature for dynamin assembly.^{6,33} In turn, dynamin has been shown to promote the membrane tubulating activity of both F-BAR³⁴ and possibly also N-BAR proteins.^{35,36} This suggests that a functional partnership between dynamin family members and BAR proteins coordinate membrane curvature with membrane fission and fusion (Fig. 1). The N-BAR proteins amphiphysin and endophilin have been shown to act as tumor suppressors,^{37,38} while several F-BAR proteins have been linked to cancer progression and metastasis of tumors.³⁷ Endophilin B1 (also referred to as Bax interacting factor 1, Bif-1) has been shown to act as a tumor suppressor by promoting EGFR downregulation.³⁹

Suppression of endophilin B1 in breast cancer cells and in HeLa cells results in a significant delay in EGFR degradation, and endophilin B1 knockdown in lung cancer cells delayed EGFR degradation and sustained receptor activation.³⁹ Suppression of Bif-1 also sustained the activation of Erk1/2, which, as mentioned previously, plays an important role in downstream signaling to promote cell growth. Unlike dynamin 2, endophilin B1 had no effect on internalization of EGFR. Instead, it was found that endophilin B1 knockdown dramatically decreased trafficking of EGFR to the lysosome. Endophilin B1 interacts with a multitude of autophagy and apoptosis players, indicating that it primarily functions downstream of dynamin in intracellular membrane remodeling events in the cell.

III. Apoptosis

There is a strong link between apoptosis and cancer.⁴⁰ Apoptosis acts to suppress carcinogenesis in events of irreparable cellular damage or oncogenic stress, and cancer may develop when the signaling pathways that promote apoptosis are impaired or inhibited. Dynamins associated with mitochondria dynamics are implicated in apoptosis and consequently various forms of cancer. Dynamin family members mediate mitochondrial fission (Drp1) and mitochondrial fusion (Mfn and Opa1).^{41–43} There is a strong link between mitochondrial shape and apoptosis. For example, Drp1-mediated fission has been shown to facilitate the activity of pro-apoptotic protein Bax, possibly by promoting oligomerization and insertion into the outer mitochondrial membrane, an event required for apoptosis,⁴⁴ while Mfn- and Opa1-mediated fusion may be inhibitory.^{44–47} Interestingly, Bax promotes both Drp1 and Mfn activity,^{44,46,48} which suggests that dynamins and Bax form a functional partnership to coordinate regulation of mitochondrial shape and the apoptosis process. As dynamin family members play important roles in controlling apoptosis, it is no surprise to find they are linked to various cancers. For example, the anticancer drug 4EGI-1 causes apoptosis and mitochondria fragmentation in glioma cells and, in agreement, the cells had decreased levels of Mfn-1 and Opa1 and increased levels of Drp1.⁴⁹ In addition, blocking mitochondrial fragmentation by Drp1-siRNA prevented the antitumor effects of 4EGI-1.⁴⁹ Moreover, small human heat-shock protein (HSPB11), which has been associated with brain tumor malignancy, inhibits cell death possibly through enhancing the inhibitory phosphorylation of Drp1, which leads to decreased apoptosis.⁵⁰ Consistent with this, others have found that the kinase inhibitor tyrphostin A9 induces cancer cell death by Drp1-mediated mitochondrial fragmentation.⁵¹ Another antitumor drug, doxorubicin, also induces mitochondrial fission through Drp1 activity.⁵² In human glioma cells, decreasing the levels of Drp1 with shRNA or with the drug Mdivi-1 induced apoptosis and inhibited tumor growth.⁵³ However, overexpression of Drp1 has also been associated with tumor growth, e.g., the increase in malignant oncocytic thyroid tumors.⁵⁴ Mfn 2 (which is also known as hyperplasia suppressor gene 2) has been shown to exert antitumor effects in a diverse set of cancer cells (lung, breast, gastric, bladder, liver).^{55–59} Mfn2 overexpression in bladder carcinoma cells significantly inhibited cell proliferation by inducing apoptosis.⁵⁸ Significant downregulation of Mfn2 was also observed in liver cancer cells and overexpression of Mfn2 inhibited proliferation of these cells and induced apoptosis by increasing the level of caspase-3.⁵⁹

Endophilin B1 is also involved in regulation of mitochondrial dynamics, and thus plays a key role in apoptosis.⁶⁰ Endophilin B1 translocates to the mitochondria during the apoptosis process and has been suggested to play a role in Bax oligomerization at sites of mitochondrial fission.⁶¹ The exact nature of the relationship between dynamins, endophilin B1, and Bax is yet unclear. Loss of endophilin B1 leads to suppression of Bax activation and inhibition of apoptosis.⁶² This effect was shown to be BAR domain-dependent, which emphasizes the role of membrane remodeling in the function of endophilin B1. Interestingly, Bax promotes endophilin B1 oligomerization and the formation of MVB-like structures via endophilin B1-mediated tubulation and vesiculation.⁶³ This further indicates a functional partnership between apoptosis proteins and membrane remodeling members of the dynamin and BAR protein families. In all, these studies show that the roles of dynamin family member Drp1, Mitofusin and Opa1, and endophilin B1 in cancer are linked to their ability to regulate mitochondrial dynamics.

IV. Autophagy

Another intracellular membrane trafficking process that is tightly coupled to cell death and survival is autophagy. Autophagy is an evolutionary conserved lysosomal degradation mechanism used for elimination of damaged organelles, mis-folded proteins, and invasive pathogens.⁶⁴ As such, it serves a housekeeping function in the cell, as well as provides nutrients during periods of starvation. The autophagy process entails the formation of the autophagosome, a double-membrane vacuole that encapsulates cargo and fuses with the lysosome to mediate cargo degradation and recycling. Autophagy has both tumor-suppressor and tumor-promoting effects. At early stages of cancer, defects in or inhibition of autophagy results in impaired degradation and removal of damaged organelles, unfolded proteins, and reactive oxygen species (ROS), which may result in activation of oncogenic signals. At later stages, cancer cells rely on autophagy for energy and nutrients needed for proliferation, which then functions as a survival factor, promoting cell proliferation and tumor progression.

There is emerging evidence linking endophilin B1 to autophagy.^{62,65} Knockdown of endophilin B1 caused a decrease in autophagosome formation and an increase in spontaneous tumors in mice.⁶² Moreover, nutrient starvation caused accumulation of endophilin B1 in the cytoplasm where it co-localized with autophagy proteins Atg5 and LC3.⁶⁶ Loss of endophilin B1 leads to inhibition of protein degradation.⁶² Endophilin B1 interacts with a number of key autophagy regulators either directly or indirectly, specifically Atg9,⁶⁷ Beclin-1, and UVRAG.^{62,66,68} Atg9 is a transmembrane protein involved in initiation of autophagosome formation.⁶⁵ Atg9 vesicles are recruited to sites of autophagy to form initial membrane vacuoles.⁶⁹ The source of these vesicles is still a matter of debate; TGN, Golgi, endosomes, and the plasma membrane have all been suggested to serve as sources for autophagosome biogenesis.^{70,71} It has been shown that Atg9 vesicles fuse with endophilin B1 vesicles at Golgi to generate a cup-shaped membrane structure^{72,73} that may be the immature autophagosome.^{66,74} Another endophilin B1 associated autophagy protein is UVRAG.⁶² Endophilin B1 and UVRAG interact to regulate the function of the Beclin-1-phosphoinositide 3-kinase class III (PI3KIII) complex. UVRAG is also involved in endosomal trafficking; it promotes fusion of EGFR endosomes with lysosomes,⁷⁵ which also

requires endophilin B1,³⁹ and promotes the formation of PI(3)P by PI3KCIII.⁶² UVRAG also facilitates HOPS complex activity, which is required for endosomal fusion and formation of the autophagosome-lysosome.³⁹ Beclin-1 is involved in the regulation of both autophagy and apoptosis. It forms a complex with phosphoinositide 3-kinase class III (also referred to as Vps34), which promotes the generation of PI(3)P, a key signaling molecule in the initiation of autophagy.⁶² Endophilin B1 promotes formation of the Beclin-1-PI3KCIII complex, while Bcl-2 acts as inhibitor.⁶⁸ Beclin-1 is mutated in many cancers,⁶⁵ and loss of Beclin-1 results in PI(3)P mislocalization, abnormal endosomes, and a decrease in EGFR degradation.⁷⁶ Moreover, endophilin B1 may indeed be crucial in the cell's decision to undergo autophagy or apoptosis; by binding to Bax and promoting a Bax-Bcl-2 interaction, Beclin-1 is released from Bcl-2 and able to initiate autophagy.⁶²

Beclin-1 has been shown to bind specific pathogens (e.g., HIV Nef, herpes vBcl-2, and M2 from influenza), leading to inhibition of autophagy and survival of the invading pathogens.⁶⁸ This exemplifies the crucial role autophagy plays in the innate immune response to intracellular pathogens. Autophagy involved in removal of pathogens is referred to as “xenophagy” and this process, beyond removal of pathogens, has important effects on the induction and modulation of the inflammatory reaction.⁷⁷ Not surprisingly, both autophagy and inflammation are involved in several steps of carcinogenesis and cancer progression.⁷⁷

Members of the dynamin family are involved in the innate immune response to pathogens.⁷⁸ Immunity-related GTPase M (IRGM) has been shown to inhibit the propagation of a number of different intracellular pathogens.⁷⁹ IRGM null mice are extremely susceptible to bacterial infection⁸⁰ and mutations in IRGM are linked to *Helicobacter Pylori* infection and gastric inflammation, which may ultimately lead to gastric cancer.⁸¹ Polymorphism in the IRGM gene has also been linked to Chron's disease, which is often the cause of colorectal cancer.⁸⁰ IRGM is linked to apoptosis and autophagy, though its exact mechanism or role in these processes is not known. IRGM localizes to mitochondrial membranes where it preferentially binds cardiolipin and participates in the regulation of mitochondrial dynamics, specifically Drp1-mediated fission.⁸² The only known binding partners of IRGM are endophilin B1 and autophagy proteins Atg5, Atg10, and LC3.⁷⁹ Thus, all proteins known to interact with IRGM regulate one of the initial steps of autophagosome biogenesis, suggesting that IRGM might contribute to the nucleation and/or the elongation of autophagosome, and that this function is likely crucial for the role of IRGM on infection.⁷⁹ While IRGM plays a protective role in cancer by promoting autophagy-mediated removal of pathogens that may otherwise give rise to inflammation, it was shown to promote melanoma cell metastasis.⁸³ This effect was shown to be linked to Rac-1-dependent F-actin polymerization, which promotes cell migration and invasion. IRGM was also shown to mediate survival of tumor cells during starvation by promoting autophagy,⁷⁴ further confirming that autophagy plays dual roles in cancer depending on the stage of disease progression. Human guanylate binding protein 1 (hGBP-1) is another dynamin family member that is known to inhibit infection and propagation of certain pathogens.^{84,85} It has also been shown to reduce tumor growth via anti-angiogenic effect by regulation of the VEGFR pathway, though the exact mechanisms are yet unknown.⁸⁶

V. Cell Cycle Regulation

Dysregulation of cell cycle progression is a key factor in initial stages of tumorigenesis. Mitofusin 2 and amphiphysin 2 have both been shown to play roles in cell cycle regulation.^{38,55} In addition to its role in mitochondrial fusion, Mfn 2 has been shown to arrest cell cycle transition from G1 to S phase in gastric tumor cells, though the exact mechanism of Mfn 2 has yet to be determined.⁵⁷ Dynamin 2 was recently suggested to control c-Myc-dependent cell growth,⁸⁷ indicating that dynamins may be general regulators of cancer development by controlling cell cycle progression, cell proliferation and growth by controlling upstream signaling pathways.

Amphiphysin 2 (also referred to as Bin1) binds c-Myc and acts as a tumor suppressor by regulating cell cycle control.⁸⁸ Many tumor cells express mutated forms of Amphiphysin 2 and expression of this protein is reduced or altered in several cancer types, including breast, colon, prostate, lung, liver, and brain cancer.^{38,89} It is believed that Amphiphysin 2 is involved in safeguarding normal cells from the powerful oncogenic effect of c-Myc overexpression. Knockdown of Amphiphysin 2 in cancer cells caused cell proliferation, survival and increase in invasive capacity. Loss of Amphiphysin 2 in mosaic mice is associated with lung and liver carcinomas. Also, Amphiphysin 2 supports T-cell mediated immune surveillance against tumors. The mechanism by which Amphiphysin 2 promotes tumor suppression is unknown, though it has been shown to promote apoptosis in cancer cells via activation of Bax⁹⁰ and is known to promote DNA repair by binding and inhibiting poly (ADP-ribose) polymerase (PARP1), a key component in base excision repair pathway via its BAR domain.⁸⁹

VI. The Actin Network and Regulation of Cell Motility

Another role of BAR proteins that links them to cancer is their ability to regulate the actin network, which controls cell migration and cell polarity.³⁷ These functions are crucial at later stages of cancer progression, for tumor invasion and tumor metastasis. Thus, BAR proteins may act to suppress tumorigenesis via participation in endocytosis, apoptosis, and autophagy, or act to promote cancer progression via their roles as regulators of the actin network. CIP4 is an F-BAR protein that plays a role in actin cytoskeleton regulation via its interaction with N-WASP.⁹¹ CIP4 and FBP17, another dynamin binding F-BAR protein, are both involved in the formation of invadopodia in breast⁹¹ and bladder cancer,⁹² and high levels of CIP4 correlate with invasive breast cancer.⁹¹

Dynamin function during various membrane trafficking events is tightly linked to the actin network.⁴ Contrary to the anticancer effects of dynamin 2, discussed above, it has also been shown that high expression levels dynamin 2 were associated with poor prognosis of prostate cancer.²⁶ This contrary role of dynamin may be associated with its role in actin polymerization.^{93,94} In fact, a recent study found that the drug DBHA, which prevents dynamin 2 stimulated GTPase activity, also suppressed migration and invasion of H1299 cancer cells.⁹⁵ This suggests that inhibition of a dynamin-dependent actin polymerization pathway results in a decreased rate of tumor invasion. In addition, another drug promoting

dynamin oligomerization, RyngoR1-23, inhibited cell migration, possibly by preventing dynamin-actin interactions.⁹⁶

VII. Conclusions

Members of the dynamin and BAR proteins families mediate membrane remodeling in the cell. Evidence is emerging that members of these proteins serve a safeguarding role, protecting the cell against cancer and infection. Remodeling of cellular membranes is a crucial cellular process involved in signaling pathways controlling cell survival and cell death, innate immunity to intracellular pathogens, regulation of cell surface receptors, and the actin network activity. In addition, their roles in membrane trafficking, dynamins, and BAR proteins are also involved in regulation of cell cycle progression, cell growth and proliferation. The exact mechanisms are not known, though the crucial roles of these proteins in fundamental cellular processes urges future investigation into these mechanisms in efforts elucidate new signaling pathways and to identify novel drug targets in the fight against cancer.

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Abbreviations

BAR	BIN/amphiphysin/Rvs
CIP4	Cdc4 interacting protein 4
FBP17	forming-binding protein 17
EGFR	epidermal growth factor receptor
VGFR	vascular epithelial growth factor receptor
ERK	extracellular signal-regulated kinase
Bcl-2	B-cell lymphoma 2
Drp1	dynamin-related protein 1
Mfn	mitofusin
Opal	optic Atrophy 1
Bax	bcl-2-like protein 4
4EGI-1	α -[2-[4-(3,4-Dichlorophenyl)-2-thiazolyl]hydrazinylidene]-2-nitro-benzenepropanoic acid

Mdivi-1	mitochondrial division inhibitor 1
MVB	multi-vesicular bodies
ROS	reactive oxygen species
Atg	autophagy associated protein
LC3	microtubule-associated protein 1A/1B-light chain 3
UVRAG	UV radiation resistance-associated gene protein
TGN	trans-Golgi network
PI3KIII	phosphoinositide 3-kinase class III
PI(3)P	phosphatidylinositol 3-phosphate
HOPS	homotypic fusion and vacuole protein sorting
IRGM	immunity-related GTPase M
hGBP-1	human guanylate binding protein 1
PARP1	poly (ADP-ribose) polymerase
N-WASP	Wiskott-Aldrich syndrome protein
DBHA	N'-[4-(dipropylamino)benzylidene]-2-hydroxybenzohydrazide

Fig. 1.

Dynamin and BAR proteins regulate pathways involved in carcinogenesis and metastasis. A closer look at cellular mechanisms involved in carcinogenesis and metastasis, namely, receptor signaling, cell migration, cell growth, cell cycle progression, DNA repair, autophagy, and apoptosis, reveal significant involvement of membrane remodeling members of the dynamin and BAR protein families. Although the exact molecular mechanisms controlling their functions in these diverse fundamental processes are not fully elucidated, this indicates that dynamins and BAR proteins may serve important safeguarding roles in the cell's fight against cancer via their membrane remodeling properties.