Membrane transport between compartments in eukaryotic cells requires proteins that allow the budding and scission of nascent cargo vesicles from one compartment and their targeting and fusion with another. Just as SNAREs are proposed to be essential for all vesicle-fusion reactions, so classical dynamins and dynamin-related proteins have a similar appeal as the essential vesicle-scion molecules. They are involved in the scission of a wide range of vesicles and organelles, including clathrin-coated vesicles (CCVs), caveolae, phagosomes and mitochondria (FIG. 1, TABLE 1). Although dynamins are not found in all budding reactions, the more places that are investigated, the more they will probably be found. The importance of dynamin was first discovered with the identification of temperature-sensitive mutants in Drosophila melanogaster that gave rise to a paralytic phenotype. The locus was called shibire after the Japanese word for ‘paralysed’ (BOX 1). The shibire gene was then discovered to encode dynamin. Dynamin had previously been characterized as a GTPase that can associate with microtubules in vitro and as a phosphoprotein in neuronal terminals. Since then, mutations that abolish the GTPase activity of dynamin have been widely used to characterize its functions.

Dynamins are generally classified as ‘large GTPases’. This is to distinguish them from the small Ras-like and other regulatory GTPases, such as the well studied α-subunits of heterotrimeric G-proteins and the translation factors of protein biosynthesis. In addition to having a larger GTPase domain, dynamin and dynamin-related proteins are distinguished from other GTPases by their oligomerization-dependent GTPase activation, their low GTP-binding affinities and the ability of many members of the dynamin family to interact with lipid membranes. There are many large GTPases in the database — even in prokaryotes — that have homology to dynamin only in the GTPase domains, and do not have the additional domains that allow for self-oligomerization, so we do not count these as dynamin-related proteins.

Subdividing the dynamin superfamily

Overall architecture. The minimal distinguishing architectural features that are common to all dynamins and are distinct from other GTPases are the structure of the large GTPase domain (~300 amino acids) and the presence of two additional domains; the middle domain and the GTPase effector domain (GED),
Coated with the protein caveolin. The plasma membrane that are flask-shaped invaginations of CAVEOLAE protein known as clathrin. Bud with the aid of a coat (CCV). Transport vesicles that CLATHRIN-COATED VESICLE from classical dynamins. Some of these proteins might be additional domains that are not complete length of the protein homology extends over the description in 1989 as ‘dynamin’, a microtubule-binding protein. For these classical proteins, the homology extends over the complete length of the protein and they have five distinct domains.

CLASSICAL DYNAMINS
Dynamins that show sequence homology to the protein described in 1989 as ‘dynamin’, a microtubule-binding protein. For these classical proteins, the homology extends over the complete length of the protein and they have five distinct domains.

DYNAMIN-RELATED PROTEINS
Dynamins that lack one or more domains or have additional domains that are not present in classical dynamins. Some of these proteins might be functionally indistinguishable from classical dynamins.

CLATHRIN-COATED VESICLE (CCV)
Transport vesicles that bud with the aid of a coat protein known as clathrin.

CAVEOLAE
Flask-shaped invaginations of the plasma membrane that are coated with the protein caveolin. Caveolae are endocytosed in a clathrin-independent manner.

REVIEWS

which are involved in oligomerization and regulation of the GTase activity (FIG. 2). The GTase domain contains the GTP-binding motifs (G1–G4) that are needed for guanine-nucleotide binding and hydrolysis (FIG. 3). The conservation of these motifs is absolute except for the G4 motif in guanylate-binding proteins (GBP; FIG. 3). The GTase catalytic activity can be stimulated by oligomerization of the protein, which is mediated by interactions between the GTase domain, the middle domain and the GED. In many of the dynamin-superfamily members, this basic set of domains is supplemented by targeting domains, such as: Pleckstrin-homology (PH) domains, proline-rich domains (PRDs) that bind to SRC-HOMOLOGY-3 (SH3) domains; or by sequences that target dynamins to specific organelles, such as mitochondria and chloroplasts. It should also be noted that alternative targeting can arise as a result of alternative splicing.

It is easy to find dynamin nomenclature confusing because the various homologues and their domains have accumulated various names, which, in some cases, overlap. In BOX 2 we highlight some of the studies on plant dynamin homologues, whereas in TABLE 2, we group dynamin and dynamin homologues across species on the basis of domain organizations. This allows us to classify proteins that have similar targeting domains together, even if the sequence homology is not close. So, Shibire, the dynamin-like protein in D. melanogaster, and Arabidopsis thaliana dynamin-like protein 6 (ADL6) are classical dynamins because they have the same domain structure as mammalian dynamin 1. It is clear that there might be further subdivisions when more targeting domains are recognized. Our classification is not based on function, and dynamins from different families and with alternative targeting domains might, therefore, have similar functions.

Overview of superfamily members

Classical dynamins. Mammalian dynamins 1, 2 and 3 are the founder members of the dynamin family. In our nomenclature we call them ‘classical dynamins’ along with other large GTPases that have the following five identifiable domains: GTase domain, middle domain, PH domain, GED and PRD (FIG. 2). Mammalian dynamin 1 is brain-enriched, where it is concentrated in the presynapse; dynamin 2 is ubiquitous (including the brain); and dynamin 3 is found in the testis, but is also brain-enriched and is found postsynaptically to 11. Web pages have been written to complement this review, giving more details on domains and mutants of dynamin 1 (see Dynamic homepage in Online links).

The single isoforms of classical dynamin in D. melanogaster and Caenorhabditis elegans are assumed to cover the functions of the multiple isoforms in mammals. Mammalian dynamins 1 and 2 have been shown to have a role in scission of CCVs. In this process, the membrane invaginates to engulf cargo into clathrin-coated pits (CCPs), which are eventually detached from the parent membrane with the aid of dynamin. However, dynamin also functions in the budding of caveolae, in phagocytosis, in the formation of podosomes, and during actin rearrangements and cytokinesis. These functions have been reviewed elsewhere26–28, and so will not be discussed further in this review. In vitro, dynamin assembles on microtubules, but there is no convincing confirmation of this interaction in vivo. The potential of the long PRD, which is absent in the dynamin-related proteins and in GBP/alsatins, to interact with many SH3 domains (BOX 3) might give this protein its versatility in working with disparate vesicle-budding pathways.

The exact function of classical dynamins will be the subject of more discussion below, but they have been described in vesicle budding as being responsible for the constriction of the lipid neck, the fission of the lipids and the regulation of the scission reaction. Whatever the exact mechanism, dynamin certainly has the potential to put energy into a thermodynamically unfavourable reaction.

Dynamin-like proteins. Compared to our five domain definition for classical dynamins, Dlps are missing the PRD. From yeast to humans, there is one Dlp homologue per organism, and this is involved in mitochondrial division18–21. There is strong evidence that Dlps oligomerise into multimers and are likely to form rings26–29. Sequence homology does not allow us to define the region between the middle domain and the...
DYNAMINS

Members of the dynamin superfamily, which include the dynamin-related proteins, Mx proteins and GBP1/Atlastin.

PLECKSTRIN-HOMOLOGOUS (PH) DOMAIN

A protein module of ~100 amino acids that is present in a range of proteins. Different PH domains interact with various phospholipids and are therefore involved in the targeting of the proteins.

SRC-HOMOLOGY-3 (SH3) DOMAIN

A protein module of ~80 amino acids that is present in a range of proteins and was first identified in the protein kinase Src. SH3 domains interact with proline-rich sequences that usually contain a PxxPxxR motif.

CLATHRIN-COATED PIT (CCP)

The initial stage of invagination of a clathrin-coated vesicle.

FUSION

The breaking of one object into parts — for example, fission of the lipiddomain membrane.

PHAGOMOPLASTIN

Dynamin-like protein found at the phagomoplast, which is the microtubular network in dividing plant cells that transports Golgi-derived vesicles to the cell plate.

CELL PLATE

A flat, membrane-bound incipient cell wall at the division plane of a plant cell. The cell plate is formed by fusion and tubulation of Golgi-derived vesicles, which results in the outward expansion, and finally fusion, of the vesicles with the side walls.

GED of Dlps as a PH domain, but this region in A. thaliana ADL2 binds specifically to phosphatidylinositol-4-phosphate (PtdIns4P)30 and might, in fact, be a PH domain. Lipid binding does not exclude the possibility that this domain is also involved in protein–protein interactions. Given the absence of a PRD, recruitment to mitochondria probably occurs through this domain.

Dictyostelium discoideum does not have a classical dynamin or a Dlp, but we have included Dynamin A (DymA) in the Dlp family. It lacks the PRD of classical dynamins and also lacks a PH domain, but instead, it has a glutamine-rich domain that is typical for proteins from D. discoideum. Deletion of DymA has pleiotropic effects, including defects in cytokinesis, organelle morphology and, to a lesser extent, in endocytosis. Therefore DymA, like other non-classical dynamins, can function in vesicle budding in addition to other membrane-sciision events.

Vps1-like proteins. Proteins within this family lack the PRD, and the region between the middle domain and GED is unlikely to accommodate a PH domain. Yeast has no classical dynamin that works in plasma membrane endocytosis, but Vps1 (vacuolar protein sorting 1) is involved in vesicle trafficking from the Golgi31,32 and probably functions as a classical dynamin homologue without the necessity for multiple targeting sequences because of its limited location. In A. thaliana, the proteins that have a similar domain architecture are homologues of soybean PHAGOMOPLASTIN, which is involved in CELL PLATE formation.

Mx-like proteins. Proteins within this family are missing the PRD and the PH domain. Expression of the human MxA and MxB proteins is induced by type I interferons and MxA gives strong protection against viral infection33,34. Fish have many interferon-induced Mx homologues and so it can be assumed that they must live in a sea of viruses. There is no Mx equivalent in D. melanogaster or C. elegans, presumably because they have not developed this mechanism to protect against infections. However, A. thaliana has an Mx-like protein. All the proteins in the Vps1 and Mx families have good conservation of the GED and GTPase domains and so these proteins show oligomerization-dependent GTPase activity (see below)35,36.

ARC5-like proteins. The A. thaliana accumulation and replication of chloroplasts mutant 5 (ARC5)-like proteins also lack the PRD and the PH domain. In plants, members of this family are involved in chloroplast division37. We have only found homologues in plants and in D. discoideum.

OPA1/Mgm1 proteins. This family of proteins, which is present from yeast to humans, has the same domain architecture as the Dlps, including a predicted PH-like domain, but has an additional amino-terminal mitochondrial import sequence that is followed by a predicted transmembrane and coiled-coil sequence. These proteins are found between the inner and outer mitochondrial membranes and are involved in mitochondrial fusion38,39.

Table 1 | Functions of dynamin-superfamily members

<table>
<thead>
<tr>
<th>Organism</th>
<th>Dynamin homologue</th>
<th>Localization</th>
<th>Function</th>
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<tbody>
<tr>
<td>Animals and yeast</td>
<td>Classical dynamins</td>
<td>Plasma membrane, trans-Golgi network and endosomes</td>
<td>Vesicle scission</td>
</tr>
<tr>
<td></td>
<td>Dlp/Dnm1</td>
<td>Mitochondrial outer membrane, peroxisomes</td>
<td>Organelle division</td>
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<tr>
<td></td>
<td>OPA1/Mgm1</td>
<td>Mitochondrial inner membrane</td>
<td>Mitochondrial fusion and division</td>
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<tr>
<td></td>
<td>Mbofusin/Fzo1</td>
<td>Mitochondrial outer membrane</td>
<td>Mitochondrial fusion and division</td>
</tr>
<tr>
<td>Yeast</td>
<td>Vps1 (a classical dynamin probably performs this function in animal cells)</td>
<td>trans-Golgi network</td>
<td>Vesicle scission</td>
</tr>
<tr>
<td>Plants</td>
<td>MxA</td>
<td>Smooth endoplasmic reticulum</td>
<td>Viral resistance</td>
</tr>
<tr>
<td></td>
<td>GBP1</td>
<td>Partially membrane associated</td>
<td>Viral resistance and antiproliferative</td>
</tr>
<tr>
<td></td>
<td>Atlastin1</td>
<td>Golgi of pyramidal neurons</td>
<td>Neural integrity, vesicle trafficking?</td>
</tr>
<tr>
<td></td>
<td>ADL1A</td>
<td>Cell-plate tubular network</td>
<td>Cytokinesis</td>
</tr>
<tr>
<td></td>
<td>ADL1C</td>
<td>Cell plate: possibly clathrin-coated-vesicle budding</td>
<td>Cytokinesis</td>
</tr>
<tr>
<td></td>
<td>ADL2A</td>
<td>Plastids</td>
<td>Chloroplast division</td>
</tr>
<tr>
<td></td>
<td>ADL2B</td>
<td>Mitochondria</td>
<td>Mitochondrial division</td>
</tr>
<tr>
<td></td>
<td>Phragmo plastin (ADL4,5)</td>
<td>Cell plate</td>
<td>Cytokinesis</td>
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<tr>
<td></td>
<td>ADL6</td>
<td>trans-Golgi network</td>
<td>Vesicle scission</td>
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<tr>
<td></td>
<td>ARC5</td>
<td>Chloroplasts</td>
<td>Chloroplast division</td>
</tr>
</tbody>
</table>

Some of the functions and localizations of classical dynamins and dynamin-related proteins are listed. ADL, Arabidopsis thaliana dynamin-like protein; ARC5, accumulation and replication of chloroplasts mutant 5; Dlp, dynamin-like protein; Fzo1, fuzzy onions 1; Mgm1, mitochondrial genome maintenance 1; OPA1, optic atrophy 1; Vps1, vacuolar protein sorting 1.
Mutations in human OPA1 (optic atrophy 1) give rise to dominant optic atrophy (DOA; box 4). The yeast homologues Mgm1 (mitochondrial genome maintenance 1) from Saccharomyces cerevisiae andMsp1 from Schizosaccharomyces pombe are clearly important in mitochondrial fusion. Mutations of Mgm1/Msp1 lead to mitochondrial fragmentation and this phenotype is suppressed by mutations in the Dlp gene of these yeast species.

Mitofusin/Fzo1 proteins. The mitofusin/fuzzy onions 1 (Fzo1) family of proteins is present from yeast to humans and has a predicted transmembrane domain in place of the PH domain. The carboxy-terminal domain is predicted to be α-helical but, other than this, its homology to the GED of dynamin is weak. This is the third dynamin-related GTPase to be involved in mitochondrial dynamics and it localizes to the cytoplasmic side of the outer mitochondrial membrane. Apparently, the coordinated fusion and fusion of organelles with several membranes is a complex event and so mitochondria are provided with three GTPases (Dlp, OPA1 and mitofusin) to coordinate fission and fusion without losing the membrane potential. However, this undoubtedly complicates the analysis of mutations in these individual GTPases.

Guanylate-binding proteins/atlastins. GBPs/atlastins might fall outside the definition for dynamin-related proteins because the GTPase domain is the only significant region of sequence conservation, but the group has been included here because the proteins have probably arisen from a common ancestor (see phylogenetic analysis in FIG. 2). The crystal structure of GBP46,47 shows intramolecular interactions that are similar to those that have been predicted for dynamins and so this structure might be a preliminary model for the GTPase, middle and GED domains of dynamin (for movies of structures see Dyma/GBP structures in Online links). The expression of GBPs is induced by type II interferon and these proteins have a role in resistance against intracellular pathogens, which is similar to, but less efficient than, that of the Mx proteins48,49. GBPs are not found in D. melanogaster or C. elegans, but there is a weak homologue in A. thaliana. Unlike dynamin, GBP can hydrolyse GTP not only to GDP, but also to GMP50. Atlastins are homologous to GBP and mutations in atlastin 1 have been identified in patients suffering from hereditary spastic paraplegia (HSP/Strümpell–Lorrain syndrome), a neurodegenerative disorder of the motor neuron system that causes progressive spasticity and weakness of the lower limbs51. The protein is associated with the cis-Golgi52. Another group of interferon-induced GBPs (p47 GBPs, which include IIGP1, see FIG. 3) shows biochemical and biological similarities to the dynamin superfamily53. However, with a size of 47 kDa, they are too small to contain all three domains and therefore were not included in our definition of the dynamin superfamily members.
Oligomerization-dependent GTPase activity. Dynamins are different to Ras-like GTPases in that oligomerization stimulates the GTPase activity once a ‘critical mass’ is reached, and the resulting GTPase activity resembles a chain reaction (there is cooperativity in the GTP hydrolysis). An oligomer normally refers to a complex of more than one monomer, but as the basic dynamin building block is a dimer or tetramer, we are using oligomerization as the ordered assembly of these building blocks into rings or helices. Ras-like regulatory GTPases do not oligomerize — their GTPase activity is stimulated by the binding of GTPase-activating proteins (GAPs). For the oligomerized (assembled) form of dynamin, dynamin itself is the GAP. To understand this GAP activity, it is important that we understand the interactions between/within dynamin molecules. Electron microscopy images of dynamin oligomers and biochemical studies have shown that the GED can interact with the GTase domain, the middle domain and also with itself. Ras-like regulatory GTPases do not oligomerize — their GTase activity is stimulated by the binding of GTPase-activating proteins (GAPs). For the oligomerized (assembled) form of dynamin, dynamin itself is the GAP. To understand this GAP activity, it is important that we understand the interactions between/within dynamin molecules.

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have been found to be specific for a certain nucleotide-bound state so far. Therefore, in this scenario, dynamin would be its own effector. However, GTP-bound dynamin can assemble more efficiently on liposomes and the assembled protein should have a higher avidity for interacting partners that contain several SH3 domains.

For further details of the importance of these residues see Oligomerization web site in Online links. I A sequences shown are for human proteins, except IIGP1, which is the mouse protein sequence. DLP1, dynamin-like protein1; GBP1, guanylate-binding protein 1; OPA1, optic atrophy 1.

The oligomerization of dynamin in low salt conditions and its ability to bind and cause tubulation of negatively charged liposomes46,49 (FIG. 4) have been used as assembly tests for other members of the dynamin family (see Oligomerization web site in Online links). Dip is a tetramer in solution and has similar domain interactions to dynamin50. Oligomerization in low salt conditions and with GTP analogues has also been shown. Dip tubulates membranes when it is overexpressed in cultured cells as well as on synthetic liposomes50. A more detailed study has been done with D. discoideum DymA, which assembles into rings and helical structures even in the absence of lipids51, and also shows cooperative GTP hydrolysis. The first dynamin-family member to be identified in plants was called phragmoplastin, and this also assembles in low salt conditions52,53.

Figure 3 | GTP-binding motifs. Only 1 GTP molecule is bound per GTPase domain, but the sequences that contribute to the interactions are spread over the domain. The key residues are shown in green. The G1 motif (in the so-called P-loop) coordinates the phosphates, whereas the threonine in the G2 motif is involved in catalysis and is hard to predict by sequence comparisons but has been confirmed experimentally in some cases. The glycine in the G3 motif forms a hydrogen bond with the γ-phosphate of GTP. The G4 motif is involved in base and ribose coordination. The oncogenic mutations in p21 Ras and the unusually conserved G4 base-coordination motif in GBPs/atlastins are shown in red. Accession numbers for proteins are as in FIG. 2 with the additions: mouse interferon inducible GTPase (IIGP)/p47 (AAF07195), human p21 Ras (P01112), human dynamin-like protein1; GBP1, guanylate-binding protein 1; OPA1, optic atrophy 1.

Box 2 | Dynamins in plants

In plants such as Arabidopsis thaliana, there are more dynamin homologues than there are in mammals, and so there is probably some functional redundancy. For example, there are at least five forms (A-E) of the A. thaliana dynamin-like protein 1 (ADL1). ADL1A and ADL1C are associated with cell-plate formation in dividing cells16,17. ADL1A is found on tubular networks at the cell plate16. In plants devoid of ADL1A, cytokinesis proceeds normally, but adl1a adl1c double mutants show defects18. ADL2A (previously called ADL2) is found on plastids, which is consistent with its amino-terminal chloroplast transit peptide19. ADL2B is localized to the constriction sites of dividing mitochondria, and expression of a dominant-negative mutant of ADL2B results in the fusion and tubulation of mitochondria, which indicates a potential role in the scission reaction20. ADL3 shares a lot of sequence identity with ADL6, but ADL6 is the only member of the dynamin superfamily in A. thaliana that has all five distinctive domains, and therefore represents a classical dynamin. Through the proline-rich domain, ADL6 interacts with the Src-homology-3 (SH3) domain of the A. thaliana protein AtSH3P3, which is a homologue of mammalian amphiphysin21. A dominant-negative mutant of ADL6 (K51E, where K51 is the equivalent of K44 in mammalian dynamin 1) causes an accumulation of lytic-vacuole-targeted cargo within the trans-Golgi network, which supports a role in trafficking from the trans-Golgi network to the vacuole22. ADL4, ADL5, At5g2080 and At2g4590 cannot be definitively sorted into the vacuolar protein sorting 1 or myxovirus-resistant protein families. However, it is clear from sequence homology that they are the A. thaliana homologues of the soybean phragmoplastins, which are also involved in cell-plate formation.

The proteins ARCS5 (accumulation and replication of chloroplasts mutant 5) and At1g3140 are more distant homologues, and ARCS5 is found on the outside of chloroplasts and is involved in their division23. No clear homologues of the optic atrophy 1 (OPA1)/mitochondrial genome maintenance 1 (Mgm1) and mitofusin/Fzo1 (fuzzy onions 1) families are found in plants, but this could be the result of low sequence homology.

A simpler set of dynamin-related proteins is present in the primitive red algae Cyanidioschyzon merolae, which contains a single chloroplast and a single mitochondrion. The dynamin-related protein C. merolae Dnm1 is involved in mitochondrial division and is a close homologue of ADL1 and ADL2. By contrast, C. merolae Dnm2 is involved in chloroplast division9,10 and shows 40% identity to A. thaliana ARCS and 25% identity to Dictostyelium discoideum AAO51595.

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Membrane binding that precedes oligomerization-dependent GTPase activity. Ras GTPase activity is controlled by GAPs, whereas the GTPase activity of dynamin is controlled by self-oligomerization. Fortunately for the cell, futile cycles of dynamin GTP hydrolysis are prevented, as the oligomerization is regulated by membrane recruitment of dynamin to its sites of action. The PH domain of classical dynamins is responsible for their interaction with negatively charged lipid membranes. The affinity of a single PH domain for head groups is low (about 1 mM for inositol-1,4,5-trisphosphate) compared to other PH domains76,77 (see PH domain web site in Online links). So the strong binding of dynamin to lipids relies on high avidity caused by the oligomerization of the protein. A single point mutation (K535A) in the PH domain of mammalian dynamin 1 has a dominant-negative effect on endocytosis in cells26,58. This low affinity of unassembled dynamin for lipids and its oligomerization after lipid binding ensures that there is tight control of GTPase activation. This feature of ‘oligomerization-dependent GTPase activity on membrane binding can now probably be extended to the dynamin superfamily. Therefore, although Dlps do not contain a bona fide PH domain, they localize to mitochondrial membranes and bind liposomes in vitro27,28. The region between the middle domain and the GED is probably involved in this. Likewise, human MxA protein is localized to the endoplasmic reticulum (ER)75. The OPA1/Mgm1 proteins have a mitochondrial targeting sequence at their amino termini (~100 amino acids), which is followed by a possible membrane insertion domain that is cleaved by a rhomboid-like protease81. They also contain a PH-like domain. So OPA1 strongly associates with mitochondrial membranes. Mitofusins/Fzo1 contain a transmembrane domain in place of a PH domain, which results in its constant attachment to the exterior of the outer mitochondrial membrane44,82. Most GBP proteins have a CaaX box (where ‘a’ is an aliphatic amino acid and X is any amino acid) for Membrane binding that precedes oligomerization-dependent GTPase activity.
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Box 3 | Dynamin-binding proteins

Dynamins function in the budding of many vesicle types. Given the low affinity and weak specificity of its pleckstrin homology (PH) domain for negatively charged lipids (see affinity measurements in PH domain in Online links) and the widespread use of dynamin in vesicle scission, many binding partners of the proline-rich domain (PRD) might target dynamin to sites of action. The PRD of classical dynamins, in which up to one in every three amino acids is a proline, can potentially interact with many Src-homology-3 (SH3) domain proteins. (Some of these are documented in the PRD domain web site in Online links.) After vesicle scission has occurred, residual dynamin remains attached to the scission site on the vesicle and at this point it might form a docking site for dynamin-binding proteins that promote polarized actin assembly, as occurs in actin comet formations.7,12,13,14

Dynamin interactions found in vitro, and SH 3-dynamin interactions tested in overexpression studies need to be verified carefully. Amphiphysin has been well studied as a dynamin-PRD-binding protein. As dynamin is a stable oligomer and full-length amphiphysin is a dimer, full-length amphiphysin will have a higher affinity for dynamin than for the monomeric isolated amphiphysin SH 3 domain. The same scenario also applies to proteins that contain several dynamin-binding SH 3 domains, for example Gb2 and intersectin, where a protein containing tandem SH 3 domains will have a higher affinity and probably a better specificity for its target sequences. Overexpression studies can lead to artefactual results because levels of expression are often 10-fold to 100-fold above normal concentrations, so any weak dynamin-binding, monomeric SH 3 domain can sequester dynamin away from its normal function in vivo. The case might be even more complex because overexpression of a dynamin-targeting protein for phagocytosis would be predicted to inhibit clathrin-mediated endocytosis and so might be called a ‘clathrin-mediated endocytic protein’. Future experiments need to carefully characterize the budding events in which dynamin-binding proteins are implicated.

Main functions of the dynamin superfamily

Vesicle scission. Classical dynamins work in many vesicle scission reactions. They are recruited by protein and lipid interactions through their PRD and PH domains. Overexpression of GTPase mutants has been widely used to investigate the involvement of dynamins in different pathways. It is now appreciated that the functions of dynamins are not limited to CCV scission (Fig. 5a), but that they are associated with many non-clathrin vesicle budding events such as caveolae budding and phagocytosis (Fig. 1)10,14. It has also become appreciated over the past few years that the mechanism of dynamin action is not clear.

Dynamin was originally proposed to act as a mechanochemical enzyme by tightening a dynamin collar around the vesicle neck after GTP hydrolysis and thereby constricting it. This was known as ‘pinchase’ activity, describing the ‘pinching off’ of vesicles, and was supported by the finding that GTP hydrolysis by dynamin on liposomes causes vesiculation. Later, the mechanochemical ‘poppase’ model was proposed, in which a helix of dynamin assembles at the neck of a vesicle and a lengthwise extension of this helix after GTP hydrolysis — caused mainly by an increase in helical pitch — results in the ‘popping off’ of vesicles from the parent membrane (Fig. 4 and, for movies, see Dynamin web site in Online links).

A fundamentally different role for dynamin in vesicle scission was presented at about the same time. This ‘regulatory’ model for dynamin function is based on comparisons with small GTPases in which a ‘catalytic arginine finger’, which is contributed by the activating protein, points into the active site and promotes GTP hydrolysis. For dynamin, it is known that self-oligomerization activates hydrolysis and so the catalytic residue is likely to be on the domain that interacts with the GTPase domain. The GED got its name from the discovery of an essential arginine residue that was shown to contribute to the GTP hydrolysis. When this arginine residue was mutated, mutant dynamin still

the attachment of an isoprenoid moiety to their carboxyl terminus, and mouse Gbp2 has been found to localize to vesicle-like structures in cells. Finally, atlastin1 has a transmembrane domain and is found on the cis-Golgi.

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the attachment of an isoprenoid moiety to their carboxyl terminus, and mouse Gbp2 has been found to localize to vesicle-like structures in cells. Finally, atlastin1 has a transmembrane domain and is found on the cis-Golgi.

Main functions of the dynamin superfamily

Vesicle scission. Classical dynamins work in many vesicle scission reactions. They are recruited by protein and lipid interactions through their PRD and PH domains. Overexpression of GTPase mutants has been widely used to investigate the involvement of dynamins in different pathways. It is now appreciated that the functions of dynamins are not limited to CCV scission (Fig. 5a), but that they are associated with many non-clathrin vesicle budding events such as caveolae budding and phagocytosis (Fig. 1)10,14. It has also become appreciated over the past few years that the mechanism of dynamin action is not clear.

Dynamin was originally proposed to act as a mechanochemical enzyme by tightening a dynamin collar around the vesicle neck after GTP hydrolysis and thereby constricting it. This was known as ‘pinchase’ activity, describing the ‘pinching off’ of vesicles, and was supported by the finding that GTP hydrolysis by dynamin on liposomes causes vesiculation. Later, the mechanochemical ‘poppase’ model was proposed, in which a helix of dynamin assembles at the neck of a vesicle and a lengthwise extension of this helix after GTP hydrolysis — caused mainly by an increase in helical pitch — results in the ‘popping off’ of vesicles from the parent membrane (Fig. 4 and, for movies, see Dynamin web site in Online links).

A fundamentally different role for dynamin in vesicle scission was presented at about the same time. This ‘regulatory’ model for dynamin function is based on comparisons with small GTPases in which a ‘catalytic arginine finger’, which is contributed by the activating protein, points into the active site and promotes GTP hydrolysis. For dynamin, it is known that self-oligomerization activates hydrolysis and so the catalytic residue is likely to be on the domain that interacts with the GTPase domain. The GED got its name from the discovery of an essential arginine residue that was shown to contribute to the GTP hydrolysis. When this arginine residue was mutated, mutant dynamin still
Our understanding of GTPases has been greatly aided by crystal structures of small GTPases bound to substrates. Here, the overall architecture of the GTPase domain is conserved and allows us to predict the residues that are essential for coordinating nucleotide binding and hydrolysis. In the figure, parts a-c show close-ups of the nucleotide-binding sites of Homo sapiens Ras, the Dictyostelium discoideum dynamin-related protein DymA and Homo sapiens guanylate-binding protein 1 (GBP1). In part d, the structure of full-length Homo sapiens GBP1 is compared to the GTPase domain of DymA. For a better comparison, the ribbon diagrams of the structures are coloured from amino- to carboxyl-terminus (green to purple) so that the corresponding regions of the proteins have the same colour. As a result, the insertions in the GTPase domains of DymA and GBP1, with respect to Ras, are easily detectable. The conserved GTP-binding motifs G1-G4 as described in Fig. 3 are shown in red. The bound nucleotide and critical residues are shown as ball-and-stick models and the catalytic magnesium as a sphere.

Part a shows the Ras structure, in which K16 coordinates the β- and γ-phosphate of GTP, and S17 and T35 coordinate magnesium binding and waters involved in hydrolysis. All these residues are conserved and their mutation leads to hydrolysis-defective GTPases. The corresponding mutations have been useful in determining the mechanism of dynamin action (see main text). The oncogenic mutations in Ras (G12V and Q61L) are not conserved in dynamin-related GTPases. Part b shows the GDP-bound form of D. discoideum DymA, in which parts of the switch regions are disordered and are shown as dotted lines. The additions and insertions in the GTPase domain shield the nucleotide from the solvent and limit the access of a possible catalytic residue from the outside. Part c shows the GBP1 structure, in which the insertions are at different positions, reflecting the distant relationship between these proteins. Again, the GTP analogue is shielded. Part d shows the DymA structure, in which a long helix extends from the core of the GTPase domain (shown in dark blue), and could act as a lever arm on GTP hydrolysis. However, from the available structures, it is hard to see how movements could be coupled to hydrolysis because, as in GBP1, this helix has no direct contact with the nucleotide-binding site.

**Box 5 | Crystal structures of GTPases**

![Image of crystal structures](https://example.com/structure.png)

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oligomerized but was defective in GTP hydrolysis. Endocytosis with this mutant was not inhibited and the authors concluded that the GTP-bound state represented the active form of dynamin that positioned other proteins for the scission reaction, and so GTP hydrolysis was not the driving force behind vesicle scission.

This regulatory model was challenged by further evidence for dynamin as a mechanochemical enzyme, showing that the hydrolysis of GTP was required for vesicle scission and that the GED contributes to the catalytic activity indirectly through oligomerization. Furthermore, using dynamin assembled on nanotubes, coupling of the GTP hydrolysis to the lengthwise extension of the dynamin helix was shown to be necessary for endocytosis.

The controversy continued with further evidence for the regulatory model when postulated ‘effector molecules’—Hsc70 and auxilin—were identified, and found to interact with dynamin exclusively in the GTP-bound state. It is important to know if these proteins interact with the GTPase domain. Both proteins have known functions in the regulation of clathrin assembly and disassembly and the authors suggested that the main role of dynamin is to recruit these effector proteins to the necks of an invaginating pit and that the formation of the clathrin coat also drives fission. This clathrin-centric model for endocytosis does not, however, take into account the role of dynamins in clathrin-independent scission events such as phagocytosis or caveolae uptake.

A crucial point is to test why other GTPase-defective dynamin mutants that are in the GTP bound state (like T65A) do not accelerate endocytosis. So this controversy is still unresolved and no doubt there will be many more interesting papers forthcoming.

We believe that the evidence presented so far for classical dynamins more strongly supports a mechanochemical model. A role for dynamin GTPases as regulators of reactions might be attractive from an evolutionary point of view, as only ATPases were previously known to carry out work. However, the fact that dynamins are the common proteins found in many vesicle scission reactions and the absence of a better scission candidate points to dynamins being the mechanochemical molecules.

**Organelle division and fusion.** Mitochondria have an inner and an outer membrane. The inner membrane is highly invaginated to form cristae and is also electrically insulated to maintain the proton gradient that drives ATP synthesis. Mitochondria undergo a constant process of fission and fusion, which ensures an appropriate distribution of mitochondria within the cell and of mitochondrial DNA in dividing cells, and might also be important in the turnover of integral membrane proteins.

It might be predicted that there are two fission molecules, one for each of the membranes in mitochondria. However, three families of dynamin-related proteins are clearly involved in mitochondrial dynamics: Dlp, OPA1...
Dlp is found at sites of constriction on mitochondria, and Dlp GTPase mutants are defective in mitochondrial division. A remarkable demonstration of the importance of Dlp in mitochondrial division came from studies of a GTPase mutant of *C. elegans*. Here, two daughter cells, which migrate after division, were found to be connected by a narrow bridge of mitochondrial membrane owing to the failure of mitochondrial division24 (FIG. 5b). This is the only mitochondrial GTPase and mitofusin (TABLES 1,2; FIGS 5b,c). Only one family, the Dlps, has been implicated in fission, whereas the others are implicated in fusion (a function which has also been seen for dynamins in plant cytokinesis; see below). All of these proteins have the GTPase, middle and GED domains, and mutations based on conserved residues in the dynamin superfamily, which have been well characterized in dynamin 1, lead to changes in the dynamic structure of mitochondria22,24,41,43,90–92.

Table 3 | Comparisons of nucleotide binding and hydrolysis

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Mammalian</th>
<th>D. discoideum</th>
<th>H. sapiens</th>
<th>H. sapiens</th>
<th>H. sapiens</th>
<th>Mammalian</th>
</tr>
</thead>
<tbody>
<tr>
<td>K_m</td>
<td>8–15 µM</td>
<td>70 µM</td>
<td>260 µM</td>
<td>470 µM</td>
<td>Irrelevant.</td>
<td>Irrelevant.</td>
</tr>
<tr>
<td>K_m</td>
<td>190–260 min⁻¹</td>
<td>26 min⁻¹</td>
<td>*27 min⁻¹</td>
<td>*80 min⁻¹</td>
<td>*Unstimulated: 0.028 min⁻¹</td>
<td>Unstimulated: 2–5 min⁻¹</td>
</tr>
<tr>
<td>K_d</td>
<td>0.2–1 µM (mGTP)</td>
<td>1 µM (mGTP)</td>
<td>1.5 µM (mGTP)</td>
<td>5 µm (GTP)</td>
<td>6–300 nM (bGTPγS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 µM (mGDP)</td>
<td>20 µM (mGDP)</td>
<td>15 µM (GDP)</td>
<td>21 µm (GDP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.3 µM (GMP)</td>
<td>29 µm (GMP)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values indicated in the table are extracted from the following references: Dynamin63,87,136, DymA29, MxA137, GBP46,138,139, Ras140,141 and Gα142,143. Fluorescently labelled nucleotides are Mant (m) and Bodipy (b). Please note that most, but not all, studies were carried out at 20°C and, where labelled with a star (*), the hydrolysis data were collected at 37°C. Catalytic rates for the dynamins are maximal figures. The total GTP concentration in a cell is 100 µM to 2 mM, of which 50–150 µM is free GTP144. The concentration of GDP is usually 10-fold lower145. Bodipy, 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene; GppNHp, β,γ-imidoguanosine-5′-triphosphate; GTPγS, guanosine-5′-O-(3-thiotriphosphate); Mant, 2′,3′-O-methylantraniloyl.

Figure 4 | Oligomerization of dynamins. a | Classical dynamins, Dlps and Mx proteins have been reported to assemble into stable dimers/tetramers26,29,68,72,132–134. This involves inter- and intra-molecular interactions of the GTPase effector domain (GED), middle and GTPase domains as illustrated in the cartoon. On the basis of electron microscopy, the building blocks for oligomeric dynamin 1 are seen as T-bar-like structures in which the pleckstrin homology domains are at the base of the T-bar, and this structure probably corresponds to the dimeric form of dynamin 1. b | Classical dynamin, Dlps and Mx all assemble in low ionic conditions or in the presence of GTP-analogues into rings and stacks of rings. These proteins induce the tubulation of liposomes that are often seen to be decorated with helical oligomers28,63,69,75. A comparison of the in vitro oligomerization and tubulation of dynamin-family members can be found on the Oligomerization web site in Online links. Nucleotide hydrolysis (in the case of dynamin 1) can lead to an increase in the pitch of the helix or to a decrease in the tubule diameter, and these are the basis for the proposed mechanical actions of dynamin. These pinchase versus poppase activities are illustrated by representative electron micrographs61,62. (See also Dynamin assembly in Online links.) The upper pannel of part b is reproduced with permission from REF. 132 © (1997) the American Society for Biochemistry and Molecular Biology. The middle panels of part b are reproduced with permission from REF. 69 © (1998) Elsevier. The lower panels of part b are reproduced with permission from REF. 69 © (1998) Macmillan Magazines Ltd.

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that is implicated in fission and so constriction of the outer mitochondrial membrane must automatically cause the constriction of the inner membrane, which leads to a simultaneous division of both membranes.

Chloroplast division also involves a dynamin, and the dynamics of other organelles such as peroxisomes involve similar molecules. All plant plastids and some mitochondria in primitive unicellular eukaryotes have maintained a homologue of the bacterial cell-division GTPase protein FtsZ that constricts the organelle by pulling the inner membrane. Two such GTPases, which are unrelated to dynamin, are also found in the D. discoideum genome, in which sequence searches have uncovered few dynamin homologues. This indicates that the FtsZ homologues might function alongside dynamins in organelle division.

As mentioned above, two mitochondrial dynamins are involved in fusion. OPA1 and its homologue in baker’s yeast (Mgm1) are processed by the inner-membrane protease that is related to rhomboid, and which cleaves off the predicted transmembrane domain. So OPA1 is found associated with the outer surface of the inner membrane and the inner surface of the outer membrane where it might link the two membranes together by oligomerization. RNA-interference-mediated loss of OPA1 causes a disorganization of the cristae structure and mitochondrial fragmentation, and deletion of the yeast protein results in a failure of mitochondria to fuse. The third mitochondrial GTPase is mitofusin and, as its name suggests, it is implicated in mitochondrial fusion. It is found on the outside of the outer mitochondrial membrane and has a membrane insertion domain. In immunoprecipitation experiments, the yeast Fzo1 homologue was found to interact with the yeast OPA1 homologue, and deletions of Fzo1 in yeast also resulted in a mitochondrial fusion defect.

Given the close association of these two mitochondrial fusion proteins, they probably function together to promote the fusion of both the inner and outer membranes. As such fusion has been shown to take place in areas of high membrane curvature, we suggest that the dynamin-related proteins provide this curvature by coordinating the constriction/tubulation of the outer and inner membranes (Fig. 1). It is easy to imagine how mitofusin molecules on opposing mitochondria could be involved in tethering and juxtaposing the fusogenic ends.

**Cytokinesis.** During cytokinesis in plants, dynamins are involved in the formation of the tubular-vesicular network (which is the precursor to the cell plate) and in the retrieval of excess membrane by vesicle budding from the cell plate as it matures (Box 2). Cytokinesis has been studied in great detail by electron microscopy. Vesicles from the trans-Golgi network fuse with the aid of a synaptotagmin-like molecule, and then form a tubular-vesicular network, in which the tubes are covered in a ‘fuzzy’ coat and contain callose (which forms the new cell wall). ADP1 or phragmoplastins are concentrated at the cell plate and are candidates for transforming the vesicles into tubules. This formation of a tubular network allows the generation of a two-dimensional structure, rather than a large vesicle that subsequently has to be flattened to form the membrane of the dividing cell. In the final stages, the tubular network is converted into a planar sheet and the membrane surface area is reduced by ~70%, which involves budding of CCVs. This formation of cytokinesis might be very specialized, but cell division in other species is equally dependent on dynamin, although it might be necessary for other purposes. In D. discoideum, for example, cell division fails in the absence of DymA, and cells remain attached by a narrow membrane bridge. In animal cells, dynamin is also involved in cytokinesis where it is important for vesicle budding from the cleavage furrow.

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**Figure 5: Functions of dynamins. a** Vesicle scission. An electron micrograph of dynamin at the constricted neck of an endocytic vesicle. Reproduced with permission from REF. 112 © (2003) National Academy of Sciences USA. **b** Mitochondrial fission. Divided cells in Caenorhabditis elegans are connected by the mitochondrial outer membrane in cells expressing the mutant Dynamin-like protein DRP1 (K40A). Reproduced with permission from REF. 24 © (1999) Elsevier. **c** Mitochondrial dynamics. Mutations in dynamin-related protein 1 (Dnm1) and fuzzy onions 1 (Fzo1) show opposite effects on mitochondrial morphology in yeast. Deletion of Dnm1 leads to a network of mitochondria, whereas deletion of Fzo1 leads to fragmentation. Reproduced with permission from REF. 135 © (2000) The Rockefeller University Press. **d** Cytokinesis. Dynamin (DymA)-deleted Dictyostelium discoideum cells fail to complete cell division and stay connected by long, narrow, cytoplasmic bridges. Reproduced with permission from REF. 25 © (1999) the American Society for Cell Biology. **e** Antiviral activity of MxA. The antiviral activity of MxA in cells transfected with MxA compared to the surrounding cells labelled for a viral protein. Reproduced with permission from REF. 34 © (2000) the American Society for Microbiology.
Antiviral activity. Mx proteins were identified in mice owing to their antiviral effect against influenza virus. No activity has been identified for Mx8, but the human MxA protein has antiviral activity against a broad spectrum of viruses. This is a remarkable activity, the exact mechanism of which is not understood, but it might be directed at several stages of the viral replication pathway and a direct and GTP-dependent interaction of MxA with viral nucleocapsids has been shown. It is known that MxA can associate with the smooth ER, through which viral proteins can pass. Furthermore, it has been suggested that the GTPase-inactive, monomeric Mx protein has anti-viral activity, which might break with the tradition that other dynamins require their GTPase activities for function. There have been suggestions that Mx proteins might interfere with dynamin functions, although there is no evidence that they can hetero-oligomerize with any dynamin. An anti-viral effect of human GBP1 has been shown, but the inhibitory effect was much weaker than that of human MxA for its target viruses. GBP1 has also been shown to have antiproliferative action in epithelial cells.

Conclusion and perspectives

How dynamins work. Dynamins carry out a broad range of functions in cell biology, but there are expected to be some underlying themes. Given the domain structures and biochemical information, it is not unreasonable to assume that oligomerization-stimulated GTPase activity will be common to all members. Does this mean that dynamins are always scission molecules? Dynamins are also found in circumstances in which scission is not required — for example, in tubulation during cytokinesis in plants, in mitochondrial fusion reactions and in podosome formation. However, most of these circumstances also involve interactions between dynamin and lipid membranes. It is possible that differences in the GTPase activity of the molecule will determine its ability to tubulate or to cause lipid fission. We already know that classical dynamins cause lipid tubulation in vivo under circumstances in which vesicle scission does not work. In a recent example of this, knockdown of clathrin expression led to overexpression of dynamin 2, which resulted in an accumulation of endocytic profiles (long tubular invaginations from the plasma membrane) that were surrounded by a dynamin helix. This is very similar to the recovery of the Shibire phenotype in the study of Kessell et al., in which long tubules appeared when the cells were moved back to the permissive temperature. Mx proteins were identified in mice owing to their antiviral effect against influenza virus. No activity has been identified for Mx8, but the human MxA protein has antiviral activity against a broad spectrum of viruses. This is a remarkable activity, the exact mechanism of which is not understood, but it might be directed at several stages of the viral replication pathway and a direct and GTP-dependent interaction of MxA with viral nucleocapsids has been shown. It is known that MxA can associate with the smooth ER, through which viral proteins can pass. Furthermore, it has been suggested that the GTPase-inactive, monomeric Mx protein has anti-viral activity, which might break with the tradition that other dynamins require their GTPase activities for function. There have been suggestions that Mx proteins might interfere with dynamin functions, although there is no evidence that they can hetero-oligomerize with any dynamin. An anti-viral effect of human GBP1 has been shown, but the inhibitory effect was much weaker than that of human MxA for its target viruses. GBP1 has also been shown to have antiproliferative action in epithelial cells.

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perturbation that rips the lipid molecules apart. So dynamin itself might adapt its biochemical properties to cause tubulation and/or fission, depending on the context.

The key to solving how dynamin work will be the structural analysis (preferably of a mammalian classical dynamin) in its various nucleotide states so that we can accurately determine what, if any, conformational changes occur on GTP hydrolysis. If a conformational change does indeed occur, this should be shown to produce a force that is capable of explaining membrane fission. An alternative biochemical approach might be to examine whether the tubulation and vesiculation abilities of dynamin are related to the speed of GTP hydrolysis and/or to the extent of a conformational change. On the other hand, if dynamin is not the scissors molecule, then it is important to identify what is. Finally, moving back into cells, we should test the importance of the speed of GTP hydrolysis on the phenotypes of various organelles by making mutants of dynamins that slow GTP hydrolysis.
References 125 and 126 show the link between dominant optic atrophy (DOA) and mutations in a dynamin-superfamily member OPA1.


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Competing interests statement
The authors declare that they have no competing financial interests.

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