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Review

Bicaudal D Family of Motor Adaptors: Linking Dynein Motility to Cargo Binding

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Transport of different intracellular cargoes along cytoskeleton filaments is essential for the morphogenesis and function of a broad variety of eukaryotic cells. Intracellular transport is mediated by cytoskeletal motors including myosin, kinesin, and dynein, which are typically linked to various cargoes by adaptor proteins. Recent studies suggest that adaptor proteins can also act as essential transport cofactors, which control motor activity and coordination. Characterization of the evolutionary conserved Bicaudal D (BICD) family of dynein adaptor proteins has provided important insights into the fundamental mechanisms governing cargo trafficking. This review highlights the advances in the current understanding of how BICD adaptors regulate microtubule-based transport and how they contribute to developmental processes and human disease.

Intracellular Transport and Motor Adaptor Proteins

Intracellular cargo transport is essential for cellular function, and many developmental and neurological diseases directly result from mutations in various components of transport pathways [1–3]. The basic transport machinery is well defined: the cytoskeleton forms a network of 'rails' that are used by molecular motors for the directed delivery of cargo, such as organelles, vesicles, protein complexes, and mRNAs. Long-range transport depends on microtubules, which are relatively long and rigid cytoskeletal filaments that serve as tracks for kinesin and dynein motors [4,5]. Individual motors move unidirectionally along microtubules, with kinesins typically translocating towards the plus end and dyneins to the minus end. Some cargoes move predominantly in one direction; however, many organelles and macromolecular complexes undergo back-and-forth movements because of the alternating activities of kinesin and dynein motors, which can remain stably associated with the cargo even when they are inactive [6–10]. The net transport and the correct cellular distribution of cargoes thus often depend on the balance between the opposing dynein and kinesin activities. The molecular mechanisms underlying motor recruitment, activation, and regulation are still poorly understood.

Various adaptor proteins that link motors to cargo have been implicated in controlling motor coordination and cargo movement (reviewed in [9–12]). Motor adaptors often represent core components of large protein complexes, which include membrane-associated cargo receptors, scaffolding factors, signaling proteins, such as kinases and GTPases, and even glycolytic enzymes (reviewed in [11,13]) (Figure 1A). Well-studied multifunctional adaptor proteins that regulate cargo transport include Milton/TRAK, Jun N-terminal kinase (JNK)-interacting proteins (JIPs), glutamate receptor-interacting protein (GRIP), Rab7-interacting lysosomal protein (RILP), and sorting nexins [14–18] (Figure 1A). Motor–adaptor complexes can integrate signaling cues, such as changes in Ca^{2+} levels, phosphorylation or Rab GTPase activity, to locally control cargo movement (Figure 1B) (reviewed in [10–12]). In this way, adaptor proteins can facilitate organelle-specific responses to the local environment changes.

Trends

Bicaudal D adaptor proteins link dynein motors to specific cargos.

Bicaudal D and related adaptors induce processive motility by stabilizing the interaction of dynein and dynactin.

Bicaudal D and related adaptors can interact with motors of opposite polarity and control their activities.

Conformational transitions in Bicaudal D may coordinate motor recruitment with cargo binding.

Missense mutations in Bicaudal D and other dynein cofactors lead to transport defects and human disease.

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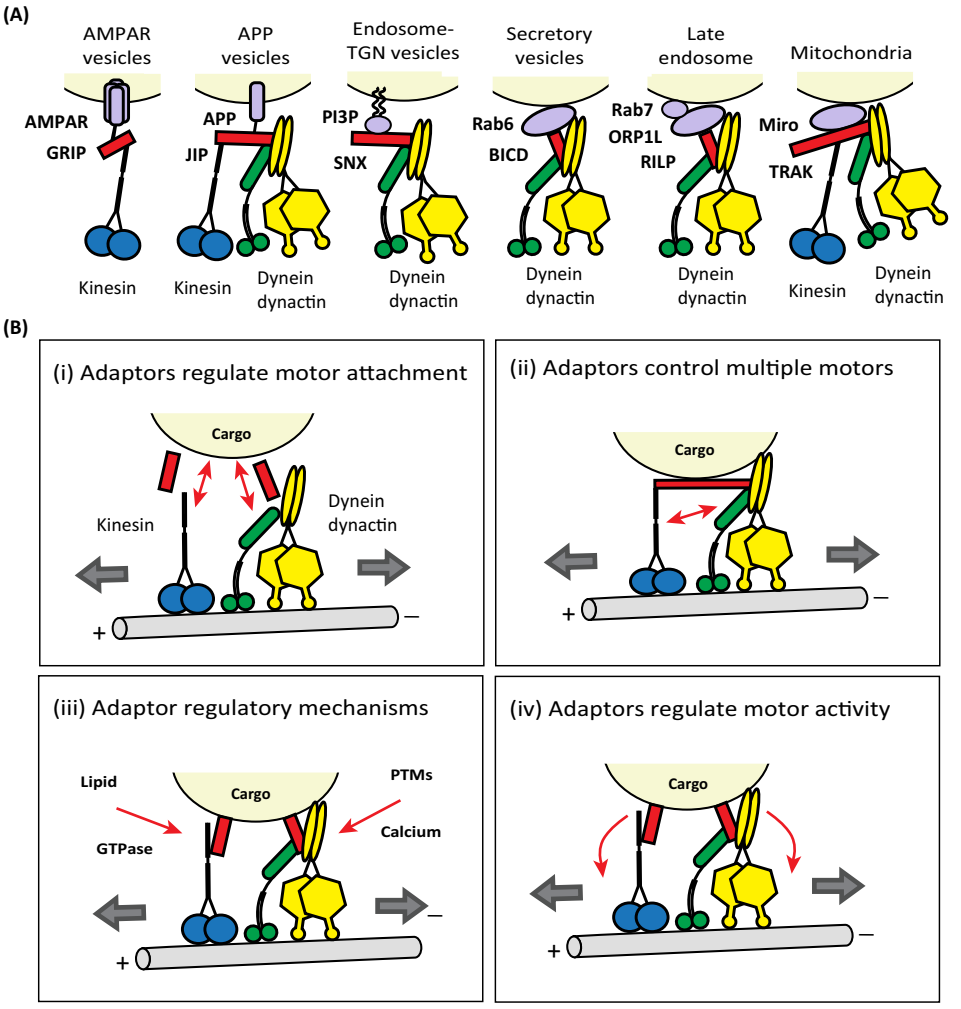

Figure 1. Current Models for Adaptor Proteins Controlling Motor–Cargo Binding. (A) Schematic diagram of various multifunctional adaptor proteins. Adaptor proteins (red) are components of large protein complexes (purple) that link kinesin (blue) and dynein/dynactin motors to various cargoes. Dynein (yellow) and dynactin (green) are indicated (for simplicity) as homodimers with two microtubule-binding domains (circles) and a long tail region (ovals). Most adaptors bind directly to the motor protein but frequently need other factors (such as receptors, membrane proteins, lipids, Rab GTPases, and small G proteins) to interact with the specific cargoes. Examples of multifunctional adaptor proteins: glutamate receptor-interacting protein (GRIP) that binds kinesin-1 and GluA2 containing AMPA receptors; Jun N-terminal kinase (JNK)-interacting proteins (JIPs) that interact with amyloid precursor protein (APP), kinesin-1, and dynein/dynactin; sorting nexin-4 that interacts with phosphoinositides and dynein; Bicaudal D (BICD) that binds to dynein/dynactin and the small GTPase Rab6; Rab7-interacting lysosomal protein (RILP) that associates with dynein, oxysterol-binding protein-related protein 1L (ORP1L); and Milton/TRAK that binds the mitochondrial Rho GTPase Miro, dynein/dynactin, and kinesin-1. (B) Basic functions for motor–cargo adaptor proteins. (i) Adaptors regulate motor attachment: in this model, adaptors interact with one type of motor, either kinesin or dynein–dynactin. If the adaptor recruits kinesin, the cargo will move unidirectionally towards the plus end of the microtubule. If the adaptor binds dynein/dynactin, the cargo will move unidirectionally towards the microtubule minus end. (ii) Adaptors control multiple motors: in this model, adaptors recruit both kinesin and dynein/dynactin motors. The cargo will move bidirectionally along the microtubule, depending on the dominant motor type (tug-of-war mechanism) or the signaling pathways that control motor activity (regulatory mechanism). (iii) Adaptor regulatory mechanisms: adaptor complexes can integrate signaling cues, such as changes in Ca^{2+} levels, phosphorylation, or other post-translational modifications (PTMs), Rab GTPase activity, or organelle-specific phosphoinositide regulation, to control motor–cargo binding and cargo motility. (iv) Adaptors regulate motor activity: in this model, adaptors can act as essential cofactors for motor activation. Bicaudal D (BICD) family proteins have recently been shown to stimulate processive dynein motility by promoting the dynein–dynactin interaction.