Cytoplasmic Dynein
It Walks The Walk

Cytoplasmic dynein is a multi-subunit motor protein powered by ATP hydrolysis that “walks” along the microtubules (MTs) of a cell’s cytoskeleton carrying cargo that is too large to diffuse such as lysosomes, endosomes, and parts of the Golgi complex. With the help of accessory proteins dynein can transport cell components as large as the nucleus. During mitosis dynein associates with the kinetochore of chromosomes and captures spindle MTs so that chromosomes can be positioned correctly. Because of this crucial role in cell division, lack of dynein is lethal for mammalian embryos and death occurs 5-7 days after fertilization. Cytoplasmic dynein assembles as a homodimeric complex consisting of a tail where cargo is attached and a force producing head known as the motor domain. The head consists of a motor domain composed of six AAA ATPase subunits arranged in a ring. In addition, the head contains two microtubule binding domains (MTBD’s) which are connected to the motor domain by coiled coil stalks. The MTBD, stalk, and motor domain form the “legs” of dynein that walk along microtubules. The stalks are composed of two anti-parallel alpha helices that can move relative to each other. Changes in conformation in the motor domain caused by ATP binding to the AAA ring are thought to be transmitted along the stalk to the MTBD causing it to be pulled off the microtubule while conformational changes in the six helices of the MTBD upon binding to the microtubule are thought to be transmitted back along the stalk to the motor domain readying it for ATP binding.

Abstract: Cytoplasmic Dynein

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The Structure of Dynein

• The two identical heavy chains of dynein each have a head, tail, stalk and a Motor Domain (MTBD). Each head is a motor domain consisting of six subunits. Subunits 1 through 4 bind ATP. ATP binding and hydrolysis in subunit 1 is required for dynein motility.
• The microtubule binding domain (MTBD) is attached to the motor domain by the stalk.
• The stalk allows two way communication between the MTBD and the motor domain.

What is Cytoplasmic Dynein?

Dynein binds to the microtubule strongly when the stalk is in the α registry (black).
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1. ATP binds to the head causing the stalk to shift to the +β registry (orange).
2. ATP hydrolysis in the head causes a shift in the stalk registry from the +β to the α registry. Dynein binds again to the microtubule.
3. Recovery stroke with bound ATP in the head.
4. ATP hydrolysis.
5. Release of ADP and Pi from the head triggers the power stroke. The proce repeats.

Cytoplasmic Dynein and Functional Role of Dynein’s Microtubule Binding Domain

Dynein Activities During Mitosis

Cytoplasmic dynein helps position and separate chromosomes.

Embryonic Cells at Metaphase

Dynein During Metaphase

1. Anchors microtubules (spindle fibers) to the cell cortex.
2. Anchors microtubules by their minus ends to the spindle poles.
3. Captures microtubules at the kinetochore of chromosomes during prometaphase and helps position chromosomes.
4. Silences checkpoint proteins by pulling them off the kinetochore allowing mitosis to proceed to anaphase.
5. Releases checkpoint proteins by pulling them off the kinetochore allowing mitosis to proceed to anaphase.

How Does Dynein Walk? One Hypothesis

1. Dynein binds to the microtubule strongly when the stalk is in the α registry (black).
2. ATP binds to the head causing the stalk to shift to the +β registry (orange).
3. Recovery stroke with bound ATP in the head.
4. ATP hydrolysis in the head causes a shift in the stalk registry from the +β to the α registry. Dynein binds again to the microtubule.
5. Release of ADP and Pi from the head triggers the power stroke. The process repeats.

Dynein’s MTBD docked on a microtubule protofilament. Helix 1 and Helix 3 interact with the microtubule between the α tubulin and β tubulin monomers. [5]

Microtubule Binding Domain

Helices 1, 3, and 6 have amino acid residues that when mutated to alanine eliminate dynein’s ability to bind microtubules. [3]

Biochemical Activities During Mitosis

Dynein’s motor (head) and MTBD binds to the minus end of microtubules and walks along the microtubule.

Embryonic Cells at Metaphase

Dynein is in the α registry (black).

MTBD