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Review Article

Kinesin superfamily proteins (KIFs): Various functions and their relevance for important phenomena in life and diseases

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ABSTRACT

Kinesin superfamily proteins (KIFs) largely serve as molecular motors on the microtubule system and transport various cellular proteins, macromolecules, and organelles. These transports are fundamental to cellular logistics, and at times, they directly modulate signal transduction by altering the semantics of informational molecules. In this review, we will summarize recent approaches to the regulation of the transport destinations and to the physiological relevance of the role of these proteins in neuroscience, ciliary functions, and metabolic diseases. Understanding these burning questions will be essential in establishing a new paradigm of cellular functions and disease pathogenesis.

Contents

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Most newly synthesized proteins in the cell are actively transported along cytoskeletal filaments to their appropriate destination by molecular motors. Proteins are transported in various membranous organelles and protein complexes, and mRNAs are carried in large ribonuclear protein complexes. Directional intracellular transport is most prominent in polarized cells, such as neurons and epithelial cells, and is fundamental for neuronal function and survival because most of the proteins required in the axon and nerve terminals must be transported from the cell body. Therefore, neurons are a good model system for studying intracellular transport. Among the molecular motors that are involved in intracellular transport, three large superfamilies have been identified—kinesins, dyneins and myosins.

Here, we focus on the role of the kinesin superfamily proteins (also known as KIFs) in the process of intracellular transport in various cell types. Based on observations made using electron microscopy, five major kinesin families were initially discovered in the mouse brain. It is now thought that there are 45 mammalian KIF genes, but there could be twice as many KIF proteins because multiple isoforms can be generated by alternative mRNA splicing. The KIFs are classified into 15 kinesin families, which are termed kinesin-1 to kinesin 14B according to the results of phylogenetic analyses (Fig. 1). These families can be broadly grouped into three types, depending on the position of the motor domain in the molecule: N kinesins have a motor domain in the amino terminal region, M kinesins have a motor domain in the middle region and C kinesins have a motor domain in the carboxy terminal region. In general, N kinesins and C kinesins provide microtubule-plus-end- and minus-end-directed motilities, respectively, and M kinesins depolymerize microtubules into tubulin molecules [1,2].

This review focuses on several important questions regarding the role of KIFs in intracellular transport. Regarding the mechanisms of intracellular transport, studies have accumulated evidence related to the types of cargo that are transported by each KIF [2]. The second question is how these KIFs recognize and bind to these cargos. It has been clarified that KIFs typically use scaffold proteins and adapter proteins to recognize and bind to cargo although they can sometimes bind to their cargo directly. The cargo–motor relationship has a high level of specificity; however, there is redundancy in some cases. The third question is how cargo unloading is controlled: phosphorylation, Rab GTPase activity and Ca^{2+} signaling were identified as their major mechanisms [1]. In this review, we focus on the fourth question, which is concerned with how the direction of transport is determined in relationship with the microtubule tracks. Furthermore, we introduce the emerging exciting roles of KIFs in the regulation of several important physiological processes in mammals, including the regulation of higher brain functions such as learning and memory, brain development, development of the body plan, and relationships with certain diseases.

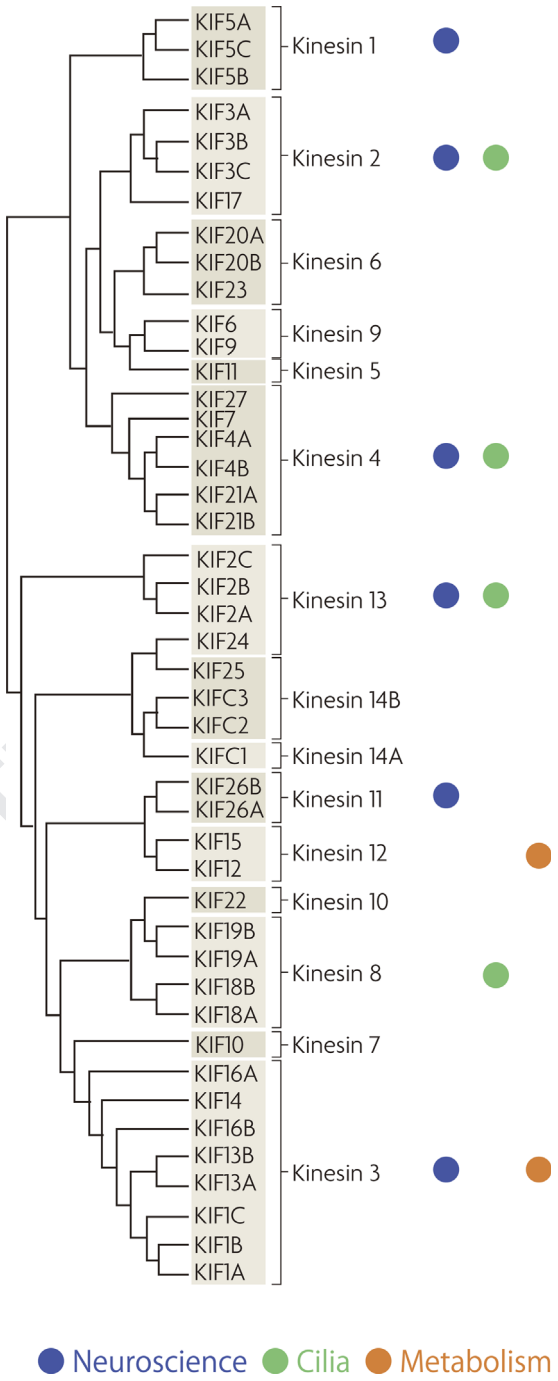

Fig. 1 – Molecular phylogeny of mouse kinesin superfamily proteins (KIFs), classified into 15 subfamilies. The significance of each subfamily in neuroscience, ciliary function, and metabolic diseases are marked as indicated, according to the text. Reproduced and modified with permission from Ref. [1].

Regulatory mechanisms of transport directions

Neurons are highly polarized cells possessing dendrites and a long axon. The differential transport of various types of membrane organelles and proteins into these polarized processes is fundamental for neuronal morphogenesis, function, and survival. Recently, it has been shown that a number of kinesin superfamily proteins, or KIFs, play significant roles in polarized transport [2]. GFP-VSV-G, beta-APP and GAP-43 are transported dominantly towards the axon by the kinesin-1 motor KIF5 whereas GFP-Kv2.1 is transported to the dendrites [3]. However, the homodimeric kinesin-2 motor KIF17 conveys NR2B-containing vesicles to the dendrites [4]. What controls this directional transport is a fundamental question in neurobiology.

As a basis of this mechanism, differences in the microtubule tracks between the axon and dendrites have been noted. In this

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