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REVIEW ARTICLE

THE ROLE OF MOTOR PROTEIN KIF4 DURING VIRAL INFECTION AND ITS CLINICAL POTENTIAL

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Abstract

Kinesin and dynein are two types of ATP-dependent mechanochemical motors that are involved in the transport of a variety of cytoplasmic cargos along microtubule fibers, the regulation of microtubule stability and the maintenance of centrosome integrity. Besides being responsible for both the maintenance of cell morphology and physiological functions, kinesins also play important roles in cell division, cell motility, spindle assembly, chromosome aggregation and separation. Although its role might be different in different types of cancer, some KIFS have been known to play a role in many types of cancer development, and they have also been pointed as interacting with viruses during viral infection, notably during viral egress. With an ongoing need for novel anti-retroviral treatments, these findings open the way for further studies with this motor protein, aiming the development of new and more efficient treatment strategies for chronic diseases such as AIDS caused by these fast-mutating viruses**.** This article presents an overview of KIF4' structure and functions and focus on its interactions with the Gag retroviral polyprotein during retroviral infection. Moreover, we draw attention to KIF's clinical potential as a therapeutic target to block retroviral infections by interfering with the production of new viral particles through microtubules' destabilization.

Introduction:-

Overview of Kif4' Structure and Functions:

KIF4 is a member of the Kinesin Superfamily Proteins (KIFs), which is a family of closely related ATP-dependent mechanochemical motor proteins that are involved in the transport of a variety of cytoplasmic cargos such as vesicular organelles, mitochondria, RNA-protein complexes, protein complexes, intra-flagellar rafts, and chromosomes along microtubule fibers, usually moving in the direction of the plus or minus end of microtubules (Miki and Hirokawa, 2013). These proteins are involved in the regulation of microtubule stability and the maintenance of centrosome integrity (Wu et al., 2008), being responsible for both the maintenance of cell morphology and the realization of physiological functions. They also play important roles in cell division, cell motility, spindle assembly and chromosome aggregation and separation (Sheng et al., 2018a). Some KIFS have been

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known to play a role in many types of cancer development although this role might differ in different types of cancer, and they have also been described as having a role in viral infection, notably during viral egress (Nelson and Guyer, 2012).

Kinesin consists of two heavy chains and several light chains. The kinesin heavy chain (KHC) consists of an NH_2-terminal globular motor domain that has an alleged ATP-binding site and a microtubule-binding site, a central α-helical coiled coil stalk domain, and a COOH-terminal fan-like domain that interacts with light chains and vesicles (Sekine et al., 1994). An ~360-residue globular domain is their main feature. This well-conserved domain contains both a catalytic pocket for the hydrolysis of ATP and the binding sites for microtubules, being often referred to as the 'catalytic core'. Most KIFs form a long filamentous structure, with the globular domain at one end and a fan-shaped structure that associates with light chains at the other end in the case of the kinesin heavy chain, as revealed by electron microscopy (Miki, Okada and Hirokawa, 2005). The catalytic core domain at one end is also called the 'head', followed by the stalk region and finally the 'tail' domain at the opposite end of the molecule. The 'head' domain is responsible for the movement driven by the hydrolysis of ATP whereas the 'stalk/tail' domain is important for the interaction with other subunits of the holoenzyme or with cargo molecules. A short region between the 'head' and 'stalk', namely the 'neck', often contains family-specific features.

KIF4 is plus-end-directed and contains a characteristic N-terminal motor domain that binds to microtubules and ATP, being responsible for force generation along microtubules. It also contains a central stalk region involved in dimerization and a C-terminal tail believed to mediate binding of cargo (Martinez et al., 2008). Its motor domain (Figure 1a) has been described by (Chang et al., 2013) as having a layer of central β-sheets between two layers of α-helices (Figure 1b), and the N-terminal of the catalytic core forming both the top α-helix and the central β-sheet layers, containing the ATPase reaction center. ATP is trapped in a shallow groove on the top surface of the catalytic core formed by the phosphate-binding loop (L4 or P-loop). The C-terminal half of the helix (α3) and the following loop (L9 or switch I) are also located near the catalytic center and contribute to the effective hydrolysis of ATP. The C-terminal half of the catalytic core forms the bottom α-helix layer that contains five structural elements: loop L11, helix α4, loop L12, helix α5, and loop L13. This region is known as switch II because of its analogy to the switch II structural element in G proteins, which serves as the binding surface for the microtubule (Figure 1b).

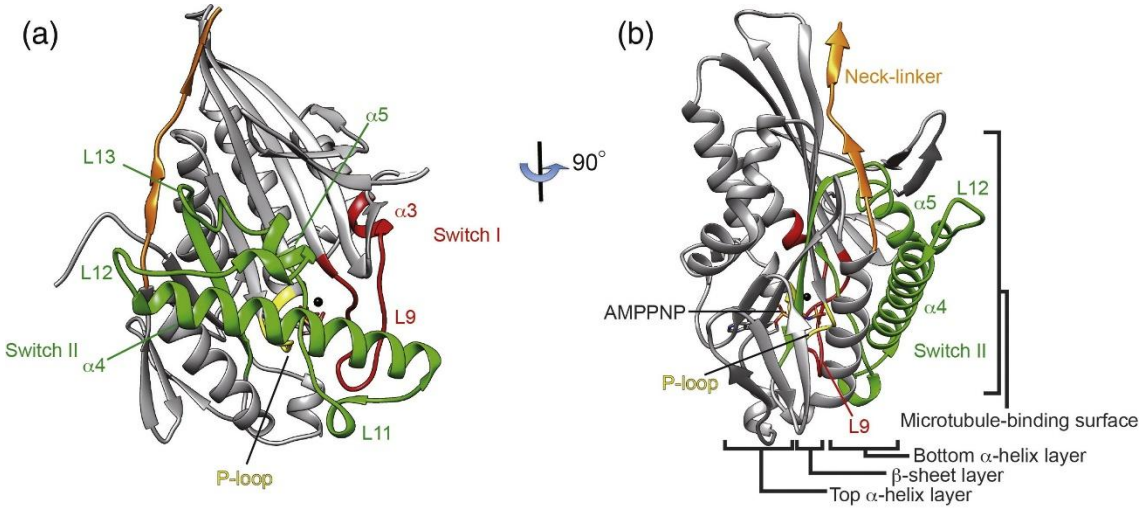

Figure 1:- Overall architecture of the KIF4 motor domain. (a) The KIF4 motor domain seen from the microtubule binding side. The P-loop, switch I, switch II, and neck linker are shown in yellow, red, green, and orange, respectively. (b) The KIF4 motor domain seen from the right side. Modified from Chang et. al (2013).

KIF4 can be found in the cytoplasm and in the nucleus and is involved in multiple intracellular events such as organelle and vesicle transport, midzone formation, chromosome segregation during mitosis and cytokinesis, regulation of the expression of vascular endothelial growth factor (VEGF) receptor 1 (VEGFR1), activation of epithelial genes, repression of mesenchymal genes, and regulation of programmed cell death in juvenile neurons (Sekine et al., 1994; Lee et al., 2001; Zhu and Jiang, 2005; Wu et al., 2008; Hu et al., 2011; Tiwari et al., 2013), highlighting its importance in intracellular trafficking and as a transcriptional regulator.

Kif4's Interactions with Gag Polyprotein During Viral Infection:

Just like our cells, viruses also need to maintain stability during their life cycle, and for that they use and manipulate the host cell's machinery for membrane trafficking, transcription, splicing, nuclear pore transport and protein synthesis (Sodeik, 2004). Almost all viruses are capable of taking advantage of their hosts' cytoskeleton to facilitate their replication and spread, with several viruses using the microtubules to transport their genetic material from the plasma membrane to the replication center of the infected cell, and, in some cases, also during viral egress of newly synthesized viral proteins from the nucleus to the plasma membrane where assembly of new virions takes place, after which they can exit the cell either through exocytosis or by budding to the plasma membrane (Radtke, Döhner and Sodeik, 2006; Sheng et al., 2018b; Zhou et al., 2018).

Stabilization of microtubules increases the efficiency of retroviral infection (Naghavi et al., 2007), and this is achieved by microtubule plus-end tracking proteins (+TIPs) that are recruited to dynamic microtubule ends by the end-binding protein EB1. (Sabo et al., 2013) has demonstrated that during HIV infection the HIV-1 matrix protein targets KIF4 that subsequently binds to the EB1 protein, therefore inducing microtubule stabilization through post-translational modifications such as detyrosination and acetylation. The EB1 protein also recruits plus-end tracking proteins (+TIPs) to the dynamic microtubule ends for regulation of the microtubule stabilization process.

The motor protein KIF4 has been shown to help maintain stability of retroviruses during infection, and most studies until the present time have been focused on human immunodeficiency virus type 1 and murine leukemia virus and their interactions with the retroviral Gag polyprotein, a very important protein that directs the assembly and release of virus-like particles from the cell (Tang et al., 1999), thus being essential for viral survival and spread. Gag polyproteins must multimerize, bind to membranes, and then assemble into a virion that is released from the cell for a viral particle to form. For the HIV-1 Gag polyprotein, the components responsible for membrane binding have been mapped to the N-terminal matrix domain and include the N-terminal myristate and a cluster of basic residues (Yuan et al., 1993; Zhou et al., 1994; Ono and Freed, 1999). KIF4 has also been shown to interact with Gag polyproteins in Simian Immunodeficiency Virus (SIV) and Mason-Pfizer Monkey Virus (MPMV) (Kim et al., 1998).

KIF4 binds to Gag polyproteins in vivo and KIF4-Gag association can be detected in normal cells infected by a retrovirus (Kim et al., 1998). Disrupting its function slowed temporal progression of Gag through its trafficking intermediates and inhibited virus-like particle production. Knockdown of KIF4 also led to increased Gag degradation, resulting in reduced intracellular Gag polyprotein levels (Martinez et al., 2008). When KIF4 is reintroduced, normal levels of virus-like particles production are restored. These studies identify a novel transit station through which Gag traffics en-route to particle assembly and highlight the importance of KIF4 in regulating HIV-1 Gag trafficking and stability, flagging Gag degradation as a unique antiviral strategy that could be exploited as a therapeutic target for intervention during HIV infection (Martinez et al., 2008).

Kif4's Clinical Potential:

The ability to genetically tag viral proteins with fluorescent proteins (FP) has advanced the study of viral entry and egress by allowing the real-time visualization of these chimeras in live cells (Nelson and Guyer, 2012). It is now possible to visualize and modify the dynamics of single motor proteins with unprecedented spatial and temporal resolutions, while structural studies have provided detailed information on the molecular conformations during the biochemical processes associated with the molecular motor motion (Kolomeisky, 2013).

Viruses can use alternative strategies for intracellular transport. One of them is to invade cytoplasmic membrane traffic. What happens is that viruses pass through the endocytic pathway to the cell center during viral entry, and after budding, virions can travel inside vesicles derived from the endoplasmic reticulum and the Golgi apparatus to the plasma membrane for viral egress. Viral components can also interact directly with the cytoskeletal transport system through direct interactions between cytosolic viral components and the cytoskeleton (Sodeik, 2004).

As pathogenic cargos, viruses require microtubules to transport to and from their intracellular sites of replication. Changes in the spatial organization and dynamics of the microtubule array mediated by virus or host-induced changes to microtubule regulatory proteins, not only play a central role in the intracellular transport of virus particles but also regulate a wider range of processes critical to the outcome of infection (Naghavi and Walsh, 2017).

KIF4 is associated with retroviral infections, including Human Immunodeficiency Virus 1 (HIV-1), Murine Leukemia Virus (MuLV), Simian Immunodeficiency Virus (SIV), Mason-Pfizer Monkey Virus (MPMV) and Rous Sarcoma Virus (RSV), mainly regarding its association with the retroviral Gag polyprotein, an essential structural component of all retroviruses and lentiviruses (Martinez et al., 2008).

Analyzing and understanding the underlying principles of KIF4's retroviral cytosolic transport can aid the design of viral vectors to be used in research as well as human gene therapy, and in the identification of new antiviral target molecules. This may lead to the identification of new targets for the development of antiviral therapy with drugs that do not inhibit viral enzymes, but specific host or virus-host interactions and are thus less likely to promote the evolution of drug-resistant viral strains.

Virus-based expression vectors should include all factors that modulate the host cytoskeleton during entry and transcription, but not those involved in virus replication and egress (Radtke, Döhner and Sodeik, 2006). According to (Elsner and Bohne, 2017), the main principle of viral vector design is the identification of viral genes or elements needed for transgene delivery and deletion of the remaining sequences to generate coding capacity for the gene of interest. In a second step, the essential genes for vector production are provided on separate plasmids yielding single-round infectious viral particles.

All retroviruses share the overall genome structure including the gag, pol, and env genes (Figure 2). Gag and pol encode the structural proteins and replication enzymes, whereas env gives rise to the envelope protein anchored in the membrane enclosing the capsid. However, complex retroviruses like lenti- and spuma viruses encode additional proteins that impact on virulence and pathogenesis (Coffin, Hughes and Varmus, 1997).

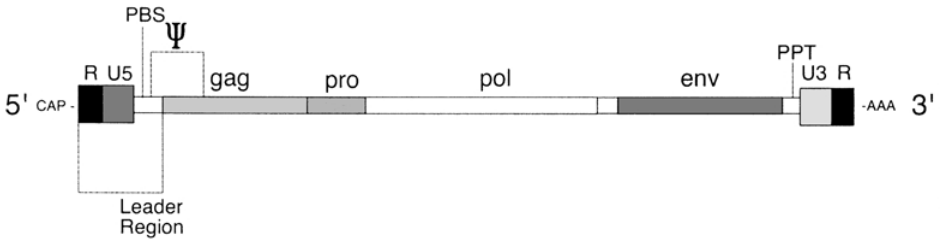

Figure 2:- Outline of retroviral genome showing the four essential coding domains: Gag, Pro, Pol, andEnv, which are found in the same relative positions in all replication-competent retroviruses. The gag domain encodes the structural components of the viral capsid (CA), matrix (MA) and nucelocapsid (NC) proteins. The pro domain encodes the viral protease (PR), while pol encodes the reverse transcriptase (RT) and integrase (IN) enzymes. The env domain encodes the surface (SU) and transmembrane (TM) glycoproteins responsible for viral attachment and penetration. Modified from Gifford and Tristem (2003).

Although the intracellular transport of Human Immunodeficiency Virus type 1 (HIV-1) Gag to the plasma membrane remains poorly understood, and cellular motor proteins responsible for Gag movement are not known, the interactions between retroviral Gag polyproteins and the kinesin motor protein KIF-4 suggest that large multi-protein complexes are translocated on the microtubule-based cytoskeleton in virus-expressing cells (Tang et al., 1999). Martinez et. al (2008) showed that disruption of endogenous KIF4 slows progression of newly synthesized Gag through its trafficking intermediates and that KIF4 might control Gag polyprotein stability. As previously mentioned, when KIF4 is disrupted, degradation of intracellular Gag is greatly increased. This example provides evidence that viral ribonucleoprotein translocation is dictated by the activities of a variety of viral and cellular proteins (Cochrane, Mcnally and Mouland, 2006)

KIF4's interactions with retroviral Gag polyproteins could mediate a plus-end-directed transport of the reverse transcription complex during entry, as well as the transport of RNA granules to the plasma membrane for assembly (Sodeik, 2004). This could lead to the identification of new targets for the development of antiviral therapy with drugs that do not inhibit viral enzymes but instead inhibit specific host or virus-host interactions, being less likely to promote the evolution of drug-resistant viral strains (Radtke, Döhner and Sodeik, 2006). All this could be potentially exploited for the development of therapeutic agents that block HIV-1 or other retroviruses viral particles production through KIF4 targeting.

Conclusion:-

And Perspectives for The Future:-

KIF4's functions were first associated with the development of neurons, andlater it has been shown to be associated with chromatin and being distributed in both nucleus and cytoplasm, being expressed in different types of cells including cancer cells and germ cells. KIF4 also showed dynamic changes throughout the cell cycle (Samejima et al., 2012; Sheng et al., 2018), being also involved in regulation of mitosis and meiosis (Kim et al., 1998; Zhu and Jiang, 2005; Shrestha et al., 2012; Nunes Bastos et al., 2013; Voets et al., 2015; Camlin, McLaughlin and Holt, 2017).

This motor protein also plays a role in other diseases besides viral infections, such as cancers and Alzheimer's Disease (Sheng et al., 2018). It has been shown to have opposite effects depending on the disease, as exemplified by its role in gastric cancer and colorectal cancer. In gastric cancer, KIF4 inhibits gastric cancer cell proliferation (Gao et al., 2011), whereas in colorectal cancer, KIF4 promotes cell proliferation and lymph node metastasis (Matsumoto et al., 2018). These studies show that KIF4 could be used as a target molecule in cancer detection, and as a new type of biological target for the treatment of cancer.

Morris et al (2014) showed that KIF4 induces selective microtubule stabilization in fibroblasts, being localized at the end of microtubules and participates in the microtubule-stabilizing pathway of Rho-mDia-EB1. The lack of this motor protein blocks the selective microtubule-induced stabilization of mDia and EB1, with the tail region of KIF4 directly interacting with the N-terminal domain of EB1 to promote cell migration (Morris et al., 2014).

Knowing that the Gag polyprotein of retroviruses and its cofactors are involved in the direct binding of KIF4, and stabilization of microtubules through the EB1 pathway is needed for an efficient infection rate (Tang et al., 1999; Martinez et al., 2008; Sabo et al., 2013), KIF4 poses as a potential target for novel anti-retroviral treatments, with HIV being a good candidate as early HIV infection requires stable microtubules.

However, many regulative mechanisms are still not well characterized, with most studies about KIF4's interactions in disease progression being about cancer. Specific mechanisms of action are still poorly understood in many diseases such as retroviral infections, and further studies about this motor protein's interactions with the cell during viral infection are still needed to help support the use of KIF4 as an anti-viral therapeutic target.

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