Zika Virus Enters Soma of Neuron through NGF/TrkA-Like Endosomal Signaling Pathway

liu wenzhong [1,2,*], li hualan[2]

[1] School of Computer Science and Engineering, Sichuan University of Science & Engineering, Zigong, 643002, China;

[2] School of Life Science and Food Engineering, Yibin University, Yibin, 644000, China;

[*] Correspondence.Wenzhong Liu, liuwz@suse.edu.cn.

Abstract

Infection with the Zika virus results in severe neurological disease in adults or congenital Zika syndrome in newborns. We employed the domain search strategy to study the Zika virus glycoprotein E in this work. The results revealed that immature E contains a NGF domain ("MNKCYIQIMDLGHMCDATMSYECPMLDEGVEPDDVDCWCNTTSTWVVYGTCHH") and is capable of interacting with TrkA. The E/TrkA complex increased E's interaction with receptors such as Axl and facilitated Zika virus endocytosis via clathrin. Rab5 retrograded transmission of Zika virus-containing E/TrkA endosomal signals to neuronal soma. Rab7 helped dissociation of E/TrkA in late acidic endosomes, and then E became mature after the NGF domain was cut. After membrane fusion with the endosome, the Zika virus was released into the neuron cell body. It showed only the immature E protein of Zika had NGF activity. The retrograde trafficking of endosomal signals (E/TrkA) similar to NGF/TrkA enabled Zika virus to infect neuronal cells. E's interference with the TrkA signal impaired neuronal cell growth and results in neuronal cell apoptosis.

Keywords: Immature Glycoprotein Enevelope; Endosome; Rab5; Rab7; PI3K

1 Background

Infection with Zika virus (ZIKV) results in neuronal cell death(1). Infection with the Zika virus (ZIKV) can result in significant neurological disorders in adults, including Guillain-Barré syndrome(2). Zika virus infection during pregnancy can result in severe birth malformations and congenital Zika syndrome(3), including microcephaly(4), brain abnormalities, and other major birth problems(5). ZIKV infection in the brain has the potential to damage oligodendrocyte development and myelination(6). ZIKV causes microcephaly and other neurological abnormalities in developing fetuses when it infects human fetal astrocytes (HFA)(7). Mitochondrial rupture and potential mitochondrial membrane damage have been seen following ZIKV infection in human neural stem cells and SNB-19 glioblastoma cell lines. Abnormal mitochondrial rupture contributes to the neuronal cell death caused by ZIKV(8). This condition may be explained by the dysregulated expression of genes and signaling pathways involved in neurogenesis and neuron formation(1). At the moment, no anti-ZIKV reagent has been approved for clinical use. Investigating how the Zika virus infects brain cells will aid in the development of vaccinations and medicines.

The Zika virus genome encodes three structural proteins (capsid, anterior membrane, and envelope (E))(9) and seven non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and

NS5)(9). The envelope protein (E) of the Zika virus (ZIKV) is found on the mature virus's surface. It is responsible for the virus's entrance into cells(10). Certain sequences of ZIKV glycoprotein envelope (E) resemble the neurotoxic West Nile and Japanese encephalitis viruses. In contrast, other sequences bear a strong resemblance to the dengue virus (DENV)(11). The flavivirus envelope protein E is a class II virus fusion protein. The fusion process is exceedingly rapid and efficient(12). As is the case with flaviviruses, the monomeric ZIKV E protein has three distinct domains: the central barrel domain I (DI), the extended dimerization domain II (DII), and the C-terminal immunoglobulin-like domain III (DIII)(13).Both E and M/prM undergo significant, pH-induced conformational changes during the infection process(14). Mature virus particles are formed after the host protease furin cleaves prM to remove the pr peptide and expose the fusion loop(14). After removing the pr peptide in the low pH environment of the endosome, the mature particles subsequently become fused and infected(14). Protein E's fusion loop (FL) is positioned at the distal end of DII and is composed of hydrophobic residues. FL penetrates endosomal membranes and initiates fusion in response to pH-dependent conformational changes(13). The E protein is a homodimer that creates an antiparallel herringbone pattern(12). It has a particular glycosylation loop(12) associated with receptor interaction. Each monomer in the mature flavivirus E protein dimer is related to its neighbors via a two-fold symmetry(15). The three E protein dimers are parallel to one another in a configuration known as a raft. The virion has a total of 30 rafts(15). The structure of the ZIKV E protein is transferred from the dimer before fusion to the trimer in the initial state of fusion(16). The trimer structure of ZIKV E's fusion beginning state is generated utilizing three dimers on the virus's surface and three-fold symmetry(16). The surface proteins have an icosahedral-like arrangement.

Zika virus is an encapsulated flavivirus that is transmitted by mosquitos. It infects cells by clathrin-mediated endocytosis (CME) and fusion with acidic endosomes(17). Zika virus requires clathrin-mediated endocytosis and the function of Rab5a(18). The activation of receptor proteins initiates clathrin-mediated endocytosis. The AP2 linker complex is then recruited to promote clathrin shell assembly and membrane niche formation(19). As the invagination progresses(20), dynein (GTPase)(21) oligomerizes around the shoot neck, separating it from the cell surface and generating intracellular vesicles. Vesicles are first transported through the actin's cortex and then along microtubules(22). The vesicle grows as it goes through the cell. Uncoated vesicles fuse or are transported to early endosomes once the clathrin coating is removed. Vesicle trafficking is regulated by Rab family small membrane GTPases(23). Confocal microscopy revealed that ZIKV particles were localized in endosomes positive for Rab5 and Rab7. Rab5 and Rab7 silencing prevent ZIKV infection(24). ZIKV particles are first carried to early Rab5+ endosomes. In contrast, late Rab7+ endosomes may provide a crucial endosomal environment for ZIKV RNA release(24). All ZIKV strains studied are sensitive to pH values between 6.5 and 6.1 and require endosome acidification to infect(18). The fusion of the Zika virus occurs in late endosomes and is pH-dependent(25). NH_4Cl, which inhibits endosomal acidification, can prevent Zika virus-containing vesicles from reaching the late stage. Instead, it transports them swiftly to the plasma membrane via a rapid circulation pathway following clathrin-mediated endocytosis(25). The export of flavivirus particles was discovered to be Lyn-dependent, implying that LC3+ secretory organelles can release vast amounts of virus in a Rab11-dependent way(26).

The viral glycoprotein E may interact with a variety of receptors. The results in diverse cells are susceptible to the virus infection(17). Zika virus infection of fibroblasts, keratinocytes, and

immature dendritic cells in humans is mediated by particular receptors such as DC-SIGN, AXL, TYRO3, and TIM-1(27). The TAM receptor AXL is the crucial receptor for Zika virus entry. It is abundantly expressed in Sertoli cells and promotes ZIKV infection by boosting virus entry and negatively regulating the antiviral state(28). The neural cell adhesion molecule (NCAM1) is a possible ZIKV receptor(29). Tyro3, Axl, and Mertk (TAM) receptor tyrosine kinases support and regulate cell growth intrinsically. They perform a range of functions in the steady-state regulation of the immune response, including controlling the expression of critical target genes(30). TAM receptors contribute to the survival, proliferation, and differentiation of neural stem cells (NSCs) by regulating the production of neurotrophic factors, most notably NGF(30). TAM receptors promote neural stem cell survival, proliferation, and neuron differentiation(30). Nerve growth factor (NGF) regulates the expression of Axl and Tyro-3 receptors and has a role in the differentiation of PC12 cells(31). Tyro3 of Axl expression in PC12 cells are induced by Nerve growth factor (NGF)(32).NGF collaborates with TrkA to promote neuronal differentiation and survival(32).

Nerve growth factor (NGF) is a protein that prevents viral reactivation in neurons(33). NGF deficiency works as a stressor on neurons. It may share a similar second messenger with heat or cold stress-induced reactivation of latent HSV-1(34). The analysis of the immunological biomarker profile during acute Zika virus infection found that CXCL10, a chemokine linked with brain injury, was overexpressed(35). Numerous viruses physically connect to and internalize cells via growth factor receptors and convey receptor tyrosine kinase signals for replication(36). It has been demonstrated that inhibiting the NGF receptor TrkA pharmacologically inhibits influenza virus multiplication(37). Through TrKA signaling, NGF promotes HIV-1 replication in primary macrophages(38). The improvement of HIV-1 reproduction by NGF occurs during the late stages of the HIV-1 replication cycle and is accompanied by an increase in viral transcription and output (38). Human rhinovirus (HRV) induces an increase in the NGF/TrkA pathway in airway epithelial cells. It enhances viral replication by enhancing HRV entrance via ICAM-1 receptors and inhibiting nasopharyngeal cell death(39). NGF is a critical component in the survival of bronchial epithelial cells during infection with a respiratory syncytial virus(40). After nerve growth factor deprivation, the primary sympathetic neuron culture includes latent HSV. It demonstrates the critical role of the nerve growth factor in extending the incubation period of HSV(41).

The secreted NGF monomers mature to form tiny homodimers(42) with a high degree of hydrophobic interaction. NGF is comprised of a neurotrophic factor produced from the brain and neurotrophic factors 3 and 4/5(43). All of these peptides have a low affinity for the p75 receptor (43). However, it has a high affinity for the tropomyosin-related kinase (Trk) receptor(44). NGF interacts with TrkA's extracellular immunoglobulin-like domain (Ig-C2)(45). NGF may aid with survival. Under acidic circumstances, the signal forms a stable compound with TrkA(46). TrkA is a plasma membrane protein that interacts with dimeric NGF in the extracellular environment. Without p75, TrkA can entirely mediate NGF endocytosis(47). NGF stimulates and increases TrkA internalization, while NGF that has been internalized degrades slowly and inefficiently. NGF is reversely endocytosed upon internalization. It supports retrograde TrkA trafficking and sympathetic neuron survival retrogradely.

NGF promotes TrkA receptor endocytosis(48). The NGF/TrkA complex is endocytosed(49) mediated by clathrin(50) or macropinocytosis(51) by pincher(52) to be internalization(53). Endosomes containing NGF/TrkA signals can undergo dynamic fusion

processes and combine with other internalized products. NGF causes the development of complexes containing activated TrkA, clathrin heavy chains (CHC), and plasma membranes(49) . Clathrin-coated vesicles (CCV) contain NGF, which binds to activated TrkA (p-TrkA) and other Ras-MAPK pathway activation components(49) . NGF communicates via the incorporation of NGF, TrkA, and activation signal proteins. Retrograde transmission of occurs via axon transport in the early endosomes(54).

NGF/TrkA signals can also be detected in axons and dendrites via Rab7 (late endosome) and Rab11 (circulating endosome)(55). In comparison, newly produced NGF/TrkA endosomes is Rab5-positive during the early phases of retrograde transport. They develope and change into Rab7-positive late endosomes nearby(56). Retrograde transport is directed toward the soma of neuron. However, it is delayed in neurons due to the great distance traveled by axons. Endosomes positive for Rab5 and Rab7 represent a parallel transport mechanism for NGF/TrkA. Continuous signal transduction is carried out by Rab5-positive endosomes, whereas degradation and down-regulation are carried out by Rab7-positive endosomes(57). The acidic environment of Rab7-positive late endosomes may result in the dissociation of NGF and TrkA. The activity renders them unsuitable for signaling endosome(58).

We employed the domain search method to determine that the Zika virus glycoprotein E has an NGF domain in this present study. E's NGF domain interacts with the TrkA endosome, promoting the fusion of the E and Axl receptors. The E/TrkA complex enhances Zika virus endocytosis via clathrin. Zika virus is delivered retrogradely to neuronal cell bodies via Rab5-mediated NGF/TrkA-like endosomal signals. E and TrkA separate during Rab7-mediated degradation of positive late NGF/TrkA-like endosomes. Through membrane fusion, the Zika virus is delivered into neuronal cell bodies.

2 Method

2.1 Data set

1. The sequences of Zika virus protein E. Protein sequences of Zika virus downloaded from UniProt data set. Glycoprotein envelope E is valid and selected. A0A7U3RTL8_Polyprotein and A0A1V0E2F5_Envelope_protein_E encoded the same Glycoprotein envelope. But A0A1V0E2F5 had too many "X" letters, which was not suitable for MEME domain search results. Therefore, we chose A0A7U3RTL8_Polyprotein as the E protein.

2. Nerve Related sequences. The nerve related sequence was downloaded from UniProt data set. Keywords is “nerve”.

2.2 The localized MEME tool of scanning for conserved domains

The analysis steps are listed as follows:

1. Downloaded MEME from the official website and subsequently install it in the virtual machine ubuntu operating system. The virtual machine was VM 15.2.

2. Downloaded the E protein sequence of Zika virus from NCBI official website.

3. Downloaded the fasta format sequence such as nerve-related ones from Uniprot official website, respectively. The search keyword was “nerve”.

4. For each sequence in all nerve-related protein, paired with each E protein sequence to generate fasta format files for MEME analysis.

5. For the files generated in Step 4, a batch of 50000 was used to create several batches, and it was considered as the limited space of the virtual ubuntu system.

6. In ubuntu, searched the conserved domains (E-value<=0.05) of E protein and nerve-related with MEME tools in batches.

7. Collected the result files of conserved domains. Then, found the domain name corresponding to the motif from the uniprot database.

8. The domains' activity of each E protein was analyzed according to the characteristics of the nerve-related protein domains.

3 Results

3.1 Zika E contains a functional NGF domain.

The NGF domain (IPR002072, PFAM: PF00243) is a protein present in vertebrates and various snake venoms. It has been shown to induce sympathetic nerves and embryonic sensory neurons to divide and differentiate. Although these proteins have little in common in terms of sequence, they all have a unique arrangement of six cysteines. These cysteines are linked to form a conformation known as the "cystine knot." These proteins are active in dimer form, whether homodimer or heterodimer. The EGF-like structure (IPR000742) first binds with high affinity to specific cell surface receptors. It then induces itself dimerization, which is required for activating tyrosine kinases in the receptors' cytoplasmic domains. Thereby it initiates DNA synthesis and signal transduction of cell proliferation. TGF_BETA 2 (IPR001839) is a growth factor that transforms. TGF- (Transforming Growth Factor) is a multifunctional peptide that regulates the proliferation, differentiation, and other functions of a wide variety of cell types. The TGF-family proteins are only active in homodimers or heterodimers. TGF- signaling pathway dysregulation can result in tumor growth. Cys_knot_C (IPR006207), the functional of the CTCK domain. It is a dimer, whether homodimer or heterodimer. They share essentially minimal sequence homology with an six-cysteine structure. These cysteines are linked to form a conformation known as the "cystine knot." It is the most recently determined crystal structure of four growth factors: nerve growth factor, transforming growth factor, platelet-derived growth factor, and human chorionic gonadotropin.

From the Uniprot database, we retrieved Zika E and nerve-related sequences. Then, using the local MEME version, we searched for E's conserved growth factor-related domains. As illustrated in Table 1, the E protein contains CTCK, NGF, EGF-like, and TGF BETA 2 domains. CTCK A and B each have four and two Cys, while NGF A, B, and E each include six, two, and two Cys. CTCK A shares sequence homology with NGF A and TGF_BETA_2 A. There is an overlap between CTCK B, NGF E, EGF-like A, and TGF_BETA_2 E. CTCK A and CTCK B are required for NGF A-E activation. The receptor binding areas of TGF_BETA_2 A-C, NGF A-C, and CTCK A are linked. NGF E, EGF-like A, and TGF_ BETA_2 are all involved in membrane fusion. This data implies that the NGF structure of E has a role in the receptor binding and membrane integration processes.

The results revealed that E contains NGF domains and is capable of interacting with TrkA. The E/TrkA complex increased E's interaction with receptors such as Axl and facilitated Zika virus endocytosis via clathrin. Rab5 retrograded transmission of Zika virus-containing E/TrkA endosomal signals to neuronal soma. Rab7 helped dissociation of E/TrkA in late acidic

endosomes.

Table 1. Growth factor related domains of Zika E

Domain	Alias	Motif	Start	End	Cys
CTCK	A	HMCDATMSYECPMLDEGVEPDDVDCWCN	165	192	4
	B	WDNWEEVPFCSHHFNKLHLKDGRSIVVPCRHQDELI	3222	3257	2
NGF	A	MNKCYIQIMDLGHMCDATMSYECPMLDEGVEPDDVD CWCNTTSTWVVYGTCHH	153	205	6
	B	NMAEVRSYCYEASISDMASDSRCP	342	365	2
	C	NNKHWLVHKEWFH	497	509	-
	D	WFFDENHPYRTWAYH	2813	2827	-
	E	WDNWEEVPFCSHHFNKLHLKDGRSIVVPCRHQD	3222	3254	2
EGF-like	A	QEWKPSTGWDNWEEVPFCSHHFNKLHLKDGRSIVVPC RHQD	3214	3254	2
TGF_BETA_2	A	MNKCYIQ	153	159	1
	B	MAEVRSYCYEASISDMASDSRCPTQGEAYLDKQSDTQ YVCK	343	383	3
	C	YYLTMNNKHWLVHKEWFHDIPLPWHA	492	517	-
	D	IEEWCCRECTMP	1102	1113	3
	E	KVRKDTQEWKPSTGWDNWEEVPFCSHHFNK	3208	3237	1

3.2 Zika E possesses ion channel activity

We separated the above search results of Zika E-related ion channel domains (Table 2). Zika E possesses B30.2/SPRY and Ion_trans domains, as shown in Table 2. B30.2/SPRY (IPR001870) is a calcium channel subunit present in the ryanodine receptor. The ion_trans (IPR005821, PFAM: PF00520) domain is present in sodium, potassium, and calcium ion channel proteins. This domain is duplicated numerous times in some Na or K channel proteins. Both B30.2/SPRY A and Ion_trans A are placed near the N-terminal to E. E's N-terminal is involved in receptor binding. Ion_trans B-C could have a role in membrane fusion. It implies that Ca2+ is involved in the receptor binding and membrane fusion of the Zika E.

Table 2. Domains of Zika E associated with ion channels

Domain	Alias	Motif	Start	End
B30.2/SPRY	A	MNNKHWLVHKEWFH	496	509
Ion_trans	A	MNKCYIQIMD	153	162
	B	CPLKHRAWNSFLVEDHGFGVFHTSVW	937	962
	C	PNYNLYIMDEAHF	1779	1791

3.3 The mature E protein from Zika is devoid of NGF action.

We downloaded the crystal structures of immature E (PDB id: 6lnu) and mature E (PDB id: 5ire) from the PDB database. The position of NGF on the two crystal structures of E is manually compared (Figure 1). As illustrated in Figure 1, Zika E (in the endosome) is already a trimer and has taken on the structural characteristice. Figure 1.A demonstrates that immature E possesses the

NGF A-B domain. As illustrated in Figure 1.B, mature E possesses only the NGF B domain. It indicates that NGF A has been depleted during the immature-to-mature transition of E. The protease furin may be used to achieve this operation of cutting.

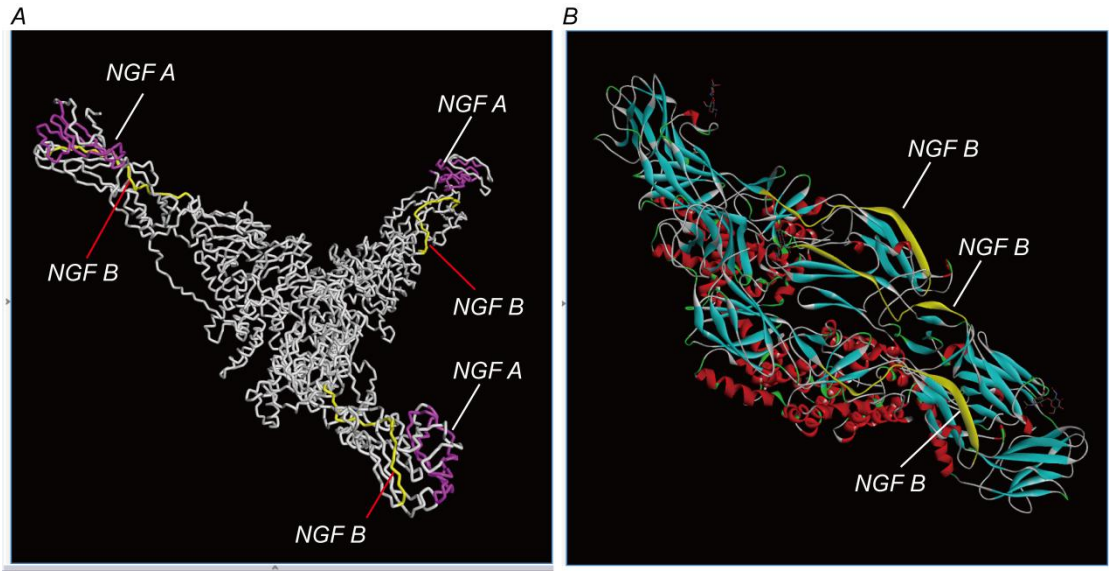

Figure 1. Zika E's NGF domains. A.The immature E's NGF domain (PDB id: 6lnu). The magenta mark represents NGF A, whereas the yellow mark represents the NGF domain of NGF B. B.The mature E's NGF domain (PDB id: 5ire). NGF B is denoted in yellow.

Zika E contains only six cysteines in the NGF A domain, which possess NGF activity. The NGF/TrkA endosomal signal can originate from the dendrites or soma of neurons. If Zika Virus lacks a regulatory mechanism, the E/TrkA-derived NGF/TrkA-like endosome signal may cause the virus-carrying endosome to travel back and forth between the soma and dendrites. It is not effective to Zika infection. Zika E matures in the low pH environment of the endosome after the host protease furin cleaves prM to reveal the fusion loop(14). It means that when the endosome containing Zika reaches the soma, the NGF domain of E loses its function owing to the endosome's acidic environment and is cut off by the protease furin. As a result, the mature E protein of Zika lacks NGF action, but the immature E protein does.

4 Discussion

4.1 The Zika virus infected neuronal cells after breaching the blood-brain barrier.

The earliest growth factors found were the nerve growth factor (NGF) and epidermal growth factor (EGF)(59). The neurotrophic factor nerve growth factor (NGF) is active in its precursor form (proNGF) outside space. It is here that maturation and degradation occur(60). NGF and other neurotrophic factors generate and release energy in target tissues(61). They activate receptors on presynaptic components innervating neurons, transmitting signals regulating survival and differentiation(62). NGF precursor translocates into the ER lumen, transporting via the exocytotic route. Then it undergoes proteolytic cleavage to change into a physiologically active mature form. Nerve growth factor (NGF) is a protein that governs the development and

responsiveness of sensory nerves and the inflammatory, immunological response(63). NGF can pass the blood-brain barrier when it binds to transferrin receptor antibodies(64).

The transfer of endosomes carrying TrkA anterogradely and retrogradely in neurons(65). TrkA is transported anterograde from somatic cells to axon growth cones via the exocytosis or transcytosis pathway(65). NGF/TrkA is endocytosed and incorporated into endocytic vesicles. Endocytosis might take place within the cell body or at the axon tip. It is transported to somatic cells for recovery or retrograde transport(65). After binding and activation by target-derived NGF, TrkA is retrogradely trafficked from the axon growth cone to the cell body(65). TrkA endosomes associate with actin regulatory proteins and mature into signaling endosomes with transport capacities. After that, the signal begins to pass the plasma membrane and enter the intracellular cytoplasm. Retrograde transport is the method by which signaling endosomes carry NGF/TrkA. The signaling molecules are carried down long axons to reach the cell bodies and dendrites(66).

Zika E was shown to have NGF activity in this present study. It suggests that Zika E may use a similar mechanism to traverse the blood-brain barrier. Then, at the synaptic or axonal terminal, Zika E/TrkA attaches and is endocytosed, forming an endosomal signal that is retrogradely delivered to the cell body. The release of the Zika virus from the endosomal body can result in infection of neural cells.

4.2 Zika E impaired neuron growth and maintenance of phenotypic

NGF is required for the growth and maintenance of neurons in the peripheral nervous system (PNS) and cholinergic neurons in the central nervous system (CNS)(67). The mature and active form of NGF is formed from the former Proteolysis of the body form (ProNGF). It is required for normal development and adulthood and possesses pro-apoptotic and neurotrophic effects (68). NGF affects the survival, differentiation, and phenotypic characteristics of hematopoietic stem cells(69)). NGF receptors are expressed in immunological organs and cell populations(69), mast cells, granulocytes, lymphocytes, and monocytes(69). In animals, NGF has been shown to ameliorate neurological abnormalities following brain injury. Protection of nerve growth factor The infant's brain is safeguarded from hypoxic-ischemic damage(70). By interacting with TrkA, NGF increases neuron survival and differentiation. TrkA initiates receptor phosphorylation and triggers signaling cascades downstream. NGF stimulates TrkA panning. The proteasome deubiquitinating enzyme trims the K63-ubiquitin chain before the TrkA receptor being transported to the lysosome for destruction following digestion and subsequent uptake into endocytic vesicles (71). The Trk receptor activates multiple small G proteins, including Ras, Rap-1, and the Cdc-42-Rac-Rho family, as well as MAP kinase(72), and phosphatidylinositol 3-kinase (PI3K)/Akt (73) . Additionally, pathways mediated by phospholipase-C (PLC-) (74). Sorting neuronal cells following TrkA endocytosis has a substantial effect on their survival and differentiation(75). NGF stimulates TrkA receptors, resulting in a brief high-amplitude burst of PI3K-Akt signaling, followed by a steady-state with a decreased amplitude(76). NGF-induced PI3K-Akt signaling is preferentially activated along axons at mitochondrial-containing locations. The route is determined by oxidative phosphorylation(76). Mitochondrial oxidative phosphorylation and glycolysis contribute to the onset and maintenance of NGF-TrkA signaling along embryonic sensory axons in distinct temporal and geographical patterns.

This study discovered that Zika E/TrkA endosomes are carried retrogradely into the cell body. In other words, ZIKA infection results in the transmission of a significant number of TrkA signals to the neuron's cell body. Thus, retrograde transport of Zika E/TrkA may result in aberrant

activation of Trk receptor signals, including those of the Ras, Rap-1, and Cdc-42-Rac-Rho families, as well as those of the MAP kinase(72), phosphatidylinositol 3-kinase (PI3K)/Akt, and phospholipase-C- (PLC-) regulated pathways. As a result, ZIKA infection can impair neuronal growth and maintenance of phenotypes.

4.3 Zika E causes apoptosis in neuronal cells

Neuron survival is associated with nerve growth factor (NGF) and its interaction with high-affinity (TrkA) and low-affinity (p75NTR) receptors. NGF induces the formation of a persistent endosomal signaling complex containing TrkA, MAPK, and Rap-1 (Ras GTPase that activates MEK/MAPK indefinitely). TrkA stimulated by NGF transiently activates Ras on the plasma membrane(77). The activation of the JNK signaling pathway and the suppression of the PI3K, Akt, and ERK signaling pathways may contribute to ZIKV-induced neuronal cell death(1). Clathrin-mediated trafficking appears to be critical for transferring information from TrkA receptor activation to Ras-MAPK pathway participation(49). Glucose variations trigger apoptosis by modulating the TrkA/p75NTR and PI3K/AKT pathways(78). The expression of the dominant-negative form of PI 3-kinase or Akt promotes apoptosis in the presence of NGF(79). By boosting proNGF and lowering mNGF, Akt, TrkA, p75 NTR, and p17, NGF and PI3K inhibition results in enhanced neuronal cell death(80). This study discovered that endosomal signals from Zika E/TrkA can be transferred to the neuron cell body. Zika infection can result in aberrant PI3K signaling, which can result in neuronal cell death.

5 Conclusion

Infection with the Zika virus (ZIKV) results in severe neurological disease in adults or congenital Zika syndrome in newborns. There is currently no authorized anti-ZIKV reagent. We employed the domain search strategy to study the Zika virus glycoprotein E in this work. The results revealed that E contains a NGF domain and is capable of interacting with TrkA. The E/TrkA complex increased E's interaction with receptors such as Axl and facilitated Zika virus endocytosis via clathrin. Rab5 retrograded transmission of Zika virus-containing E/TrkA endosomal signals to neuronal soma. Rab7 helped dissociation of E/TrkA in late acidic endosomes. The mature E protein of Zika lacks NGF action, but the immature E protein does. After membrane fusion with the endosome, the Zika virus was released into the neuron cell body. The retrograde trafficking of endosomal signals (E/TrkA) similar to NGF/TrkA enabled Zika virus to infect neuronal cells. E's interference with the TrkA signal impaired neuronal cell growth and results in neuronal cell apoptosis.

Declarations

Ethics approval and consent to participation

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets and results supporting the conclusions of this article are available at: https://pan.baidu.com/s/1LNGICUIlwJ0YoldfTv4gQA ; code：2f6m
Or: https://mega.nz/folder/p64klDDQ#vc-mXz7w9OTKGNvIA7raEg

Competing interests

The authors declare that they have no competing interests.

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Author's contribution

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Author details

[1] School of Computer Science and Engineering, Sichuan University of Science & Engineering, Zigong, 643002, China.
[2] School of Life Science and Food Engineering, Yibin University, Yibin, 644000, China.

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