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"A TRIP Back in Time to TRIP"

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Abstract

TRAF-interacting protein (TRIP, TRAIP and RNF206) was initially known as a binding partner that prevented NF-kβ activation. Currently, it is defined as a protein encoded as TRIP gene in humans. TRIP gene encodes an amino acid that has N-terminal RING finger motif. The same murine protein associates with TNFR-linked factor 1 also known as TRAF 1. It also interacts with TRAF 2 and cylindromatosis. The association with TRAF 2 leads to cell activation such as NF-κB activation. Tumor Necrosis factor receptor (TNFR) associated factors are primary adapter molecules in the TNF-signaling pathway and induce a wide range of biological processes including cell proliferation, activation, differentiation, and apoptosis. TRIP can also be defined as a novel binding protein that detrimentally influences and regulates the NF-KB activation via the TNFR2- and CD30 signaling complexes. Nonetheless, studies show that TRIP being part of several processes such as DNA stability and cell cycle progression by direct association with other binding partners is not evidence enough for its integral role. Irrespective of TRIP, being an influencing factor in cell signaling and human diseases, the physiological importance and the exact role of TRIP is not clear. As such, the review seeks to demystify, and explain the role of TRIP in various signaling pathway based on recent published research.

Keywords: Apoptosis; Cell proliferation; Mitosis; TRIP; TNFR; RAP80

Overview

The studies report that TRIP is a negative factor in down-regulation of proinflammatory cytokine production through the TNF-induced NF-κB activation. More so, TRIP is used in pathways and processes like protein-protein interactions, TNF-induced signaling pathway, ubiquitination Assays, TNF-induced Signaling Pathway, TNF-induced p65 Nuclear Translocation Assay, Real-time PCR Analysis, Enzyme-linked Immunosorbent Assay (ELISA), Cytokine Expression Array, and Statistical Analysis. Furthermore, it acts as a regulator of TNF-induced inflammatory response. TRAF2 has a RING domain that participates in ligase activity. TRIP is also used in preventing Lys63-linked TRAF2 Ubiquitination through engagement of TNF receptor associated factor and TRAF-interacting protein. Similarly, TRIP destructively regulates ubiquitination mediated by TRAF-2. Additionally, it negatively affects TNF-induced NF-κB activation via the prevention of a RING domain in ligase. The research shows that TRAF-interacting protein is imperative in the activation through down-regulation of p65 phosphorylation. Moreover, TRIP is a factor in human disease and a sky-binding partner. Studies mention that TNF receptor-associated factor (TRAF)-interacting protein (TRIP) is a novel SyK-binding partner. Other than being a binding partner, TRIP is a factor in the pathogenesis of human diseases. TRIP-deficient mouse models have laid the basis to understand the roles of TRIP in the pathogenesis of human diseases. TRIP is also a key partner in DNA damage response. In fact, previous researches discovered that TRIP is found in DNA replication compartments particularly in DNA damage responses. Further studies show that TRIP also influences mitosis. According to Lee et al., TRIP acts as a novel binding agent of RAP80. It uses a yeast two-hybrid system. As such, it plays a critical role in the conscription of RAP80 to deoxy-ribonucleic acid lesions. Therefore, TRIP is a significant factor in different signaling processes and pathways.

Introduction

Tumor necrosis factor receptor (TNFR)-associated factors (TRAFs) are key adaptor molecules in the TNF-signaling pathway and induce a wide range of biological processes including cell proliferation, activation, differentiation, and apoptosis. TRAF members directly interact with the TNFR super-family via their cytoplasmic domains [1]. Cytoplasmic domains of TNFR lack catalytic activity and possess no significant homology to each other or other known proteins [2]. To date, TRAF1-7 has been identified. Except for TRAF7, other TRAF members possess a conserved TRAF domain which is composed of (~230 amino acid length) TRAF-N and TRAF-C domain which plays a pivotal role in TRAF signaling complexes by interacting directly via cytoplasmic regions of TNFR superfamily. It is now clear that TRAF-N domain mediates the interaction with different intracellular signaling molecules. TNFR super-family members recruit several types of signal transducer molecules which have been identified to initiates different signaling pathways. Moreover, one class of signal-Transducing molecules are recruited to Fas (CD90) or TNFR1 via their death domain. For example, through their respective Death domain interactions, Fas (CD95) and TNFR1 recruit FADD (MORT1)/RIP or TRADD/FADD/RIP. Association of these signal transducers lead to the recruitment of FLICE/MACH and finally causes cell death [3].

Tumor necrosis factor receptor (TNFR)-associated factors (TRAFs) are second class of signal transducers, recruited by TNFR superfamily via their cytoplasmic interactions and either activates or suppresses the NF-Kb or JNK pathway. The ability of TRAF's to bind TNFR2, CD30, CD40, and LT-BR has been identified by their biochemical studies. The interaction of these receptors with TRAFs occur directly via a short stretch of amino acids within cytoplasmic tails, but don't interact

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with proteins contains Death domains [4]. TRAF-interaction Protein (TRIP) a signaling molecule directly associated with TRAF1 and TRAF2 proteins leads to downstream inhibition of NF-kB inhibition. TRIP is composed of 469 amino-acids with annotated domains including an N-terminal E3 Ubiquitin ligase activity Ring Finger motif followed by Coiled-coil and Leucine Zipper domain that is engaged in the TRAF-mediated signaling [5]. Initially, TRIP has been recognized as TNF interacting protein by Yeast Two-hybrid assay, directly interacts with the TRAF1 and TRAF2 proteins, which leads to the inhibition of NF-kB activation. TRIP has emerged a novel binding protein which negatively regulates the NF-KB activation through the TNFR2- and CD30 signaling complexes. TRIP plays multifunctional roles in antiviral response, cell proliferation, and apoptosis. However, recently, it has been shown that TRIP is more related to DNA stability, cell cycle progression by direct interaction with other binding partners. The critical role of TRIP in Cell cycle progression, DNA repair pathways, DNA damage response and embryonic development, have increased our interest in exploring how TRIP interact with different binding partners. Despite being involved in cell signaling and human diseases, the physiological significance and precise role of TRIP have not been yet clearly known. TRIP is a member of RING-type E3 Ubiquitin ligase family that undergoes autoubiquitination, but no studies have shown clearly its physiological functions and its substrates like NOPO a Drosophila homolog of human gene encoding TRIP till now. The E3 ring domain is followed by the Coiled-Coil and Leucine zipper domain which is critical for the protein-protein interaction. Different studies were carried to find out which domain of the protein is critical for the protein-protein interaction. However more need to be done about this protein signaling complexes. Moreover, the response shown by N-terminal RING domain of TRIP for degradation of TBK1 is mediated by ubiquitination and has been shown to be involved in TLR3/4- and RIG-I–mediated IFN-β signaling and antiviral responses [4].

Role of TRIP in Different Signaling Processes

TRIP in TRAF signaling pathway

Initially, TRIP has been reported as the binding partner of TRAF1 and TRAF2 in a Two-Hybrid screen, suppresses the NF-ƙB activation by directly binds to the TRAF1 and TRAF2 without an unseen mechanism. Members of the tumor necrosis factor (TNF) family elicit a diverse range of biological responses including cellular proliferation, differentiation, and apoptosis. The tumor necrosis receptor (TNFR) and toll-like receptor (TLR) family are signaling pathways in which TRAF proteins play important roles in the immune system and acts as a key adaptor signaling molecules which govern downstream signal. To date, TRAF1-7 has been identified in mammals. Various studies have been shown that TRIPCC is important for the interaction of CC domain of TRAF1 and TRAF2 and have shown negatively regulates the activation of NF-Kβ as shown in Figure 1. This inhibition is independent of the E3 Ubiquitin ligase activity and occurs probably by interference with receptor recruitment of TRAF proteins [6]. The Lung cancer development is associated with the TRAF family members, specifically TRAF6 promoted the cell death of lung cancer cells [7]. Moreover, TRAF2 through the interaction with TRAF interacting protein with a forkhead associated (FHA) domain (TIFA) associated with a signal transduction leads the lung cancer development [8-10].

TRIP in RAP80 signaling pathway

Receptor-associated protein 80 (RAP80) is one of the elements in BRCA1-A complex [11]. Its role is to recruit BRCA1 to DNA lesion locus in deoxy-ribonucleic acid in ubiquitin signaling pathway. It is needed for BRCA1 and BRCC36 localization of DSBs [12]. According to Lee et al., TRIP acts as a novel binding agent of RAP80 through a yeast two-hybrid system. The results of the study revealed that TRAIP is one of the upstream controllers for RAP80. As such, it plays a critical role in the conscription of RAP80 to deoxy-ribonucleic acid lesions in a proper way. This happens with the presence of an identified K-63-lined polyubiquitin appreciation at the locus of deoxy-ribonucleic acid damage. When there is no damage to the DNA, both TRIP and RAP80 are retained. The retention of both happens in PML nuclear bodies. However, when there is DNA damage, TRIP might translocate RAP80 to where the damage has occurred. It does so through the guidance of RNF20–RNF40 complex which is integral in H2B ubiquitination at the locus of DNA damage. Because of this, TRIP ends up conscripting BRCA1 complex next to the locus DNA damage occurred [13]. It does this by interrelating with RAP80 allowing DNA lesion checkpoint and the HR repair. The lack of RNF8/168 regulation by deleting TRIP lead to the localization of 53BP1. Nonetheless, when TRIP is not present, then the translocation of RAP80 takes place. Hence, the downstream

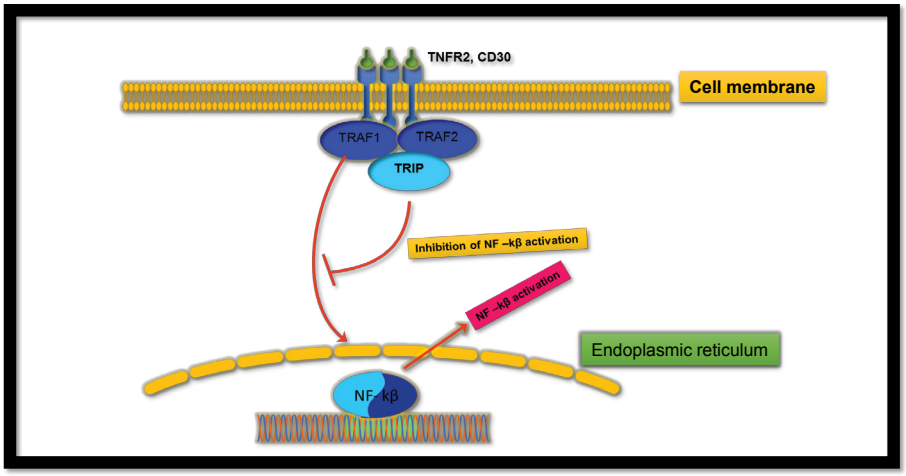

Figure 1: Role of TRIP in TRAF2 mediated NF-KB signaling pathway leading to either cell activation or cell death in NF-KB signaling pathway. TRIP interacts with TRAF1 and TRAF2 via CC domain and inhibit the function of TRAF1 and TRAF2.

targets of RAP80 are conceded for its retention at the damage locus. Therefore, it can be said the localization of RAP80 is directly dependent on TRIP even in the absence of Deoxy-ribonucleic acid lesions. As such, it can be concluded that TRIP has a controlling function on RAP80 particularly in PML nuclear bodies [2]. The findings from the research revealed that TRIP transports RAP80 from PML nuclear bodies to the locus where the damage had occurred. This happens through the interaction with one of the domains of TRAF-interacting protein. It also happens because of the interaction with C-terminal region ZF of RAP80 [14]. Nonetheless, if there is deletion of C-terminal, RAP80 mutant finds it difficult in assembling at the DNA damage locus. It will only undergo a slow translocation to the damaged sites showing that TRIP is important in altering recruitment accumulation because of the DNA lesions.

TRIP in cell cycle process or mitosis

Besides having an integral role as a novel binding agent of RAP80, TRIP also influences mitosis. Mitosis is a kind of cell division that leads to two daughter cells having similar number and types of chromosomes as parent nucleus. Cell division in mitosis involve many processes including chromosome separation. Proper chromosome separation in mitosis is temporally and spatially undertaken by set systems. Limitations in the checkpoints are the cause of errors happening during chromosome segregation and aneuploidy. As such, it ends up encouraging and fostering tumorigenesis [15]. According to this research, TRIP at most times is located near mitotic chromosomes. Cells that do not have TRIP tend to bypass taxol-induced mitotic arrests and illustrates lowered kinetochore levels of MAD2; this, however, does not happen on other spindle checkpoint proteins that have nocodazole [16]. These findings show that TRIP governs the spindle assembly checkpoint. It also regulates the proper cellular distribution of chromosomes, hence, aiding mitosis [6]. Moreover, research further reveals that TRIP is imperative for cell proliferation and organismal development. Even though TRIP is in most cases known as a negative regulator, it can be used in genome stability maintenance which is particularly arrested in mitosis [6]. This concept is further augmented by the inactivation of DNA lesions checkpoint kinase enhanced by nopo-related phenotypes giving an aspect that the cells maybe related, to some degree, to mitosis. It also portrays a relation to under-replicated DNA [6]. Nonetheless, the evaluation showed that TRIP plays an important role DNA replication procedure. It is significant to know that mitotic indices of TRIP removal cell populations maybe not be different from the control cells.

TRIP in DNA damage response

In previous researches, it was discovered that TRIP is found at DNA replication compartments particularly in DNA damage responses [17]. According to Harley, Murina, and Jackson (2016), TRIP supports DNA damage response particularly in genome replication. TRIP relocalizes the locus of DNA lesions, where it is needed for optimal phosphorylation of H2ACX and RPA2 in the S-Phase. It is needed for effective cell cycle development and mutations in TRIP, hence, lower cellular proliferation. So, human genetics states that TRIP is a component of deoxy-ribonucleic damage response (Harley, Murina & Jackson 2016). Moreover, many researchers have identified TRIP as a factor that participates in the recruitment of polymerase eta into the locus of DNA damage [18]. It is a factor said to interact with the Y-family translesion deoxy-ribonucleic polymerases. At the C-terminus, TRAIP has a motif that locates itself on deoxy-ribonucleic lacerations or DNA under duress. They also relocalize to γH2AX-marked DNA abrasions. It marks PCNA to enable its change from chromatin. Other than this, TRIP has a direct role in DNA synthesis. Research reports that the inactivation of TRIP lead to a detrimentally affected DNA synthesis in nucleotide insufficiency [19]. This, in turn, leads to the hindrance of genome stability. The research also discovered that TRIP is an important factor in mammalian replicative stress reaction network. It is also significant in the dynamic PCNA change as it fosters proper and genuine duplication of the genetic material. Remarkably, TRIP proteins are said to be found in large quantities in the nucleoli which is the storage point for numerous DDR proteins. This brings about the probability the E3 ubiquitin ligase signature motif being an agent of offering a structural scaffold aiding in the localization of TRIP in the subcellular chambers. From this perspective, it is safe to report that TRIP insufficiency may lead to a rise in the micronuclei development rate. Nonetheless, the re-introduction of TRIP leads to the decline in the formation [20]. Further reports will show that TRIP has a direct role in the replicative functions responses.

TRIP as a SyK-binding partner

TNF receptor-associated factor (TRAF)-interacting protein (TRIP) was identified a novel binding partner of SyK non-receptor protein tyrosine kinase by yeast two hybrid assay. The C-terminal region of TRIP mediates this interaction and strengthen the interaction with TNF and tyrosine phosphorylation of SyK on the treatment of cells. SyK is a tumor suppressor which regulates the malignant progression of breast cancer and expressed in normal breast epithelia. In breast cancer cells, interaction of TRIP with SyK will lead to the opposing effects on the TNF signaling pathway [21]. Activation of NF-KB is raised by Sky while TRIP suppress the activation of NF-KB. Phosphorylation at tyrosine residues of activated Sky by TNF-α promotes its binding to TRIP. Furthermore, binding of activated SyK to TRIP causes phosphorylation of TRIP. In breast cell cancer lines, the ectopically co-expressed TRIP and SyK co- localized in cytosolic punctuate complex in a small percentage of cells. The increased level of punctate complexes by TNF-α suggesting that SyK might facilitate the nuclear export of TRIP as it has been reported in previous studies to shuttle between the cytoplasm and nucleus.

TRIP in human diseases

Studies from mouse models with TRIP-deficient have shown the basis to understand the role of TRIP in the pathogenesis of human diseases [22]. By possessing their importance in regulating the embryonic development, proliferation and cell survival in different cell types, the aberrant functions of TRIP may lead to the different diseases. TRIP ablation results in early embryonic lethality in mice [5]. As shown previously that TRIP interacts with the tumor suppressors such as SyK and CYLD are involved in the formation of skin appendages such as cylindroma, trichoepithelioma and spiradenoma for CYLD and melanomas and breast tumors for both CYLD and SyK. In basal cell carcinomas and in multiple breast epithelial cell lines, an increased expression of TRIP with oncogenic potentials ranging from non-malignant to highly invasive. Rheumatoid arthritis (RA) is a kind of chronic inflammatory disorder, that eventually result the destruction of cartilage and bone [23]. Studies have shown that TRIP expression in RA-FLS was impaired as compared with osteoarthritis- (OA-) FLS and activation of NF-κB signaling was significantly inhibited by overexpression of TRIP which subsequently decreased the production of pro inflammatory cytokines and matrix metalloproteinases (MMPs) in TNFα-stimulated RA-FLS. In addition, it has been reported that interaction of TRIP with transforming growth factorβ-activatedkinase1

(TAKI) lead to the K48-ubiquitination and degradation of TAK1 in RA-FLS. Therefore, TRIP has anti-inflammatory effects on RA-FLS. Moreover, homonymous mouse dies shortly after the implantation due to defective proliferation and massive apoptosis.

Role of TRIP in other signaling pathways

According to many researches carried out recently, it was discovered that TRIP plays an integral role in a number of signaling pathways. Some of the pathways that mentioned are an antiviral response, cell proliferation, apoptosis, and embryonic development. This has elicited a great interest in trying to discover more pathways that TRIP participates in. One of the researchers discovered that TRIP can participates in the TNFR-signaling pathways [4]. The study showed that TRIP negatively takes part in the TNF-induced inflammatory response. This happens via the regulation of cytokine production. TRAF2-TRIP interface prevents Lys63-linked TRAF2 ubiquitination through deterring TRAF2 E3 ubiquitin (Ub) ligase activity. The interaction of the two elements led to the prevention of sphingosine 1-phosphate that in turn hamper ligase activity [4]. Therefore, TRIP is a negative regulator of proinflammatory cytokine production because prevents TNF-induced NF-κB activation.

Furthermore, TRIP acts as a regulator of TNF-induced inflammatory response. TRAF2 has a RING domain that participates in ligase activity. Its participation is since it has E3 ubiquitin which has the capability of Lys63-linked autoubiquitination [24]. This, in turn, triggers the activation of downstream adaptors. In this process, TRIP acts as a regulator of TRAF2-mediated NF-κB activation. It is an inhibitor in the activation through an interface with TRAF1/2 that happens in CD30 signaling multiplexes [25,26]. Other than this, it is evident that TRIP also engages in cell proliferation and survival. This is done by direct protein interaction with CYLD; though the interaction is somewhat debatable [27,28]. Nonetheless, the physiological effect and the exact role of TRIP in TNF-induced inflammatory responses have not been properly recognized. In one of the studies, researchers noted cellular and molecular mechanisms in the regulation of the activation through interaction of TRAF2-TRIP. The researchers assessed whether the interaction prevented TRAF2 ubiquitination via subduing the tie of S1P to TRAF2 E3 Ub ligase [4,29]. They concluded that TRIP is a negative factor in the down-regulation of proinflammatory cytokine production because it prevents TNF-induced NF-κB activation. TRIP is also used in pathways like protein-protein interactions, TNF-induced signaling pathway, ubiquitination Assays, TNF-induced Signaling Pathway, TNF-induced p65 Nuclear Translocation Assay, Real-time PCR Analysis, Enzyme-linked Immunosorbent Assay (ELISA), Cytokine Expression Array, and Statistical Analysis. TRIP prevents Lys63-linked TRAF2 Ubiquitination through engagement of TNF receptor associated factor and TRAF-interacting protein [4]. The expression of TRIP in the HeLa cells leads to the prevention of TRAF2 Ubiquitination. On the contrary, TRIP-KD fostered TRAF2 Ubiquitination triggered by TNF. On the other hand, TRAF2 Ubiquitination caused by the overexpression of the same factor is prevented by the introduction of TRIP [30]. TRIP also participates in TRAF2 ubiquitination assay. According to research, it prevents the pathway. The N-terminal TRIP is said to hamper ubiquitination. However, this is not the same case with C-terminal TRIP mutant. Moreover, the Ubiquitination is not impacted by non-TRAF2-binding mutant. What inhibits TRAF Ubiquitination are the coiled-coil domain. Likewise, the inhibition is also a result of leucine zipper domains of TRIP. The researchers noted that the deletion of the RING domain did not lead to any significant changes in TRAF2-mediated NF-κB activation. The same results were noted in TRAF2-TRIP interaction [4,31]. The entirety of this paper, therefore, concludes that the prevention of the activation by TRAF-interacting protein is arbitrated by the subdual of Lys63-linked TRAF2 ubiquitination through an interaction of the two factors. Similarly, TRIP destructively regulates ubiquitination mediated by TRAF-2 [32]. One of the researches mentioned that the interaction of TRAF2-TRIP prevents ubiquitination, but it does not hinder the recruitment of RIP1 to TRAF2 [4]. Additionally, the binding of SIP to TRAF2 is prevented by the TRAF-interacting protein [4]. The study concluded that TNF-SIP induced activation is moderated by TRAF-interacting protein overexpression. Additionally, TRIP negatively affects TNF-induced NF-κB activation via the prevention of a RING domain in ligase. Other than this, TRAF-interacting protein prevents Phosphorylation and Nuclear Translocation of p65 TNF ligation. Hence, TRIP influences TNF-induced signaling pathway [4]. After the stimulation, significant processes and phosphorylation are promoted in a time-dependent manner. The research shows that TRAF-interacting protein is imperative in NF-κB activation through down-regulation of p65 phosphorylation. The role of TRIP has been reported in Anteroventral periventricular nucleus (AVPV), a nucleus present larger in females and typically critical for releasing Luteinizing hormone in females, and apoptosis induced causes the sex differences in size and function in the (AVPV), in developing male [33]. It was reported that higher expression of TNF receptor associated factore-2 (TRAF2) inhibiting protein (trip) was found in males and prevented the activation of TNF-α dependent NF-Kβ and bcl-gene expression [33-36].

Conclusion

TRIP plays different roles in various signaling processes. In TRAF signaling pathway, it acts as a binding partner in Two-Hybrid screen inhibiting NF-κB activation. In the RAP80 signaling pathway, TRIP acts as a novel binding agent of RAP80 through a yeast two-hybrid system. One of the studies showed that TRIP is one of the upstream controllers for RAP80. So, TRIP plays a critical role in the conspiration of RAP80 to deoxy-ribonucleic acid lesions in a proper way. Furthermore, in the event of DNA damage, TRIP might translocate RAP80 to where the damage is located. Besides being a novel binding agent, TRIP supports DNA damage especially in genome replication. It relocalizes the location of DNA lesions and is needed for effective cell cycle development and mutations in TRIP. TRIP is also a sky-binding partner, participates in pathogenesis of human disease, and embryonic development. Additionally, TRIP is part of other signaling pathways and processes such as protein-protein interactions, TNF-induced signaling pathway, ubiquitination Assays, TNF-induced Signaling Pathway, TNF-induced p65 Nuclear Translocation Assay, Real-time PCR Analysis, Enzyme-linked Immunosorbent Assay (ELISA), Cytokine Expression Array, Statistical Analysis, mitosis, and DNA damage response. The accumulated data of TRIP *in vitro* and *in vivo* will further help to elucidate the molecular mechanism of TRIP on TRAF2 mediated NF-KB signaling which is an unanswered open question in TRAF-mediated biology. Moreover, the recent roles of TRIP in DNA damage response need to be fully addressed and which domain of TRIP inhibits the TRAF-mediated NF-KB activation need to be confirmed.

Author Contribution

The author being the sole contributor of this work and approved it for publication.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be constructed as a potential conflict of interest.

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