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Recognition of TRAIP with TRAFs: Current understanding and associated diseases

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ABSTRACT

TNF receptor proteins were primarily recognized as adaptor proteins that ligate with the tumor necrosis factor receptor (TNFR)-associated factor (TNFR) family to execute various signaling pathways. However, recent studies showed that they act as a signal-transducing molecules and are reported to have a functional role as a Toll/interleukin-1 receptor family member. Seven members of this family have been identified to date. Among TNF receptor family, TRAF7 does not share a common TRAF domain homology. The tumor necrosis factor receptor associated factor (TRAF) domain comprises of about 230 amino acid motif at the C-terminal region that has the capability to bind TNFR and execute different downstream signaling pathways. Moreover, N-terminal RING and ZINC finger constituted by the tumor necrosis factor associated protein 2 and tumor necrosis factor associated protein 6 are critical and execute various downstream signaling events. TRAF proteins have emerged as critical regulators that provide the cellular response to stress and lead to cell death. Nuclear factor kappa beta (NF-KB) and c-Jun N-terminal kinases (JNK) pathways are activated through tumor necrosis factor associated protein 2, tumor necrosis factor associated protein 5 and tumor necrosis factor associated protein 6 members. TRAF proteins in pathogenesis were observed from their abnormal expression in diseased tissue and in normal tissue, suggesting its important role in physiological processes. Recently, unique specificity of TRAF4 for glycoprotein Ibβ (GPIbβ) and glycoprotein VI (GPVI) in human platelets has been reported. The multifunctional effects of TRAIP (TNF) interacting protein in many cellular signaling pathways emerged as very important signaling molecule. Furthermore, the new insights into the structure of TRAF members along with new studies involved in health and disease prompted to explore their role particularly the TNF receptor associated proteins with novel inhibitor protein TRAIP (TNF) interacting protein and human diseases associated with it. As such, this review emphasis on tumor necrosis factor receptor associated proteins, present their current understanding with novel inhibitor protein TRAIP (TNF) interacting protein.

1. Introduction

Members of the TNF receptor superfamily emerged as the key adaptor proteins that possess the C-terminal TRAF domain and have been implicated in various critical signaling pathways. The important role of TRAF domain have been considered from its cell surface receptor interaction and other known accumulated signaling molecules (MacEwan, 2002). They were first recognized to interact with the cell surface receptor, (TNFR-2) (Chan et al., 2003). Various receptors engaged in important processes such as regulating cell death, survival and cellular response to stress interacted with their adaptor proteins (Elmore, 2007). The 45kd novel protein known as TRAF1 was identified through co -immunoprecipitation with human TNF receptor 2 (TNFR2) in cytotoxic T-cell line transfected into murine interleukin -2 and from cell lysate of CT6 by a GST fusion protein possessing the region of TNFR2 required for signal transduction (Speiser et al., 1997). Another related 56kd protein (TRAF2) was identified to interact straight with the TNFR1 cytoplasmic domains (Au and Yeh, 2007). Since then five more members of this family were identified (TRAF3, TRAF4, TRAF5, TRAF6 and TRAF7) in human and mouse. Furthermore, one TRAF in nematode *Caenorhabditis elegans* and two TRAFs in *Drosophila melanogaster* have been reported respectively (Pujol et al., 2001). The

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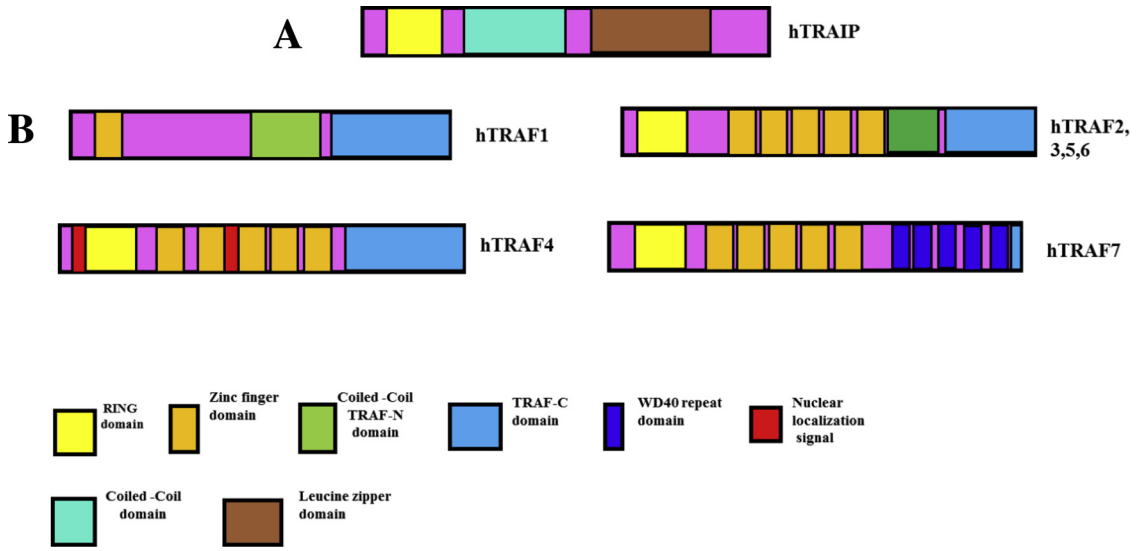

Fig. 1. Structural representation of human TRAIP and TRAF proteins. (A) hTRAIP protein consists N-terminal RING followed by a protein- protein interacting Coiled Coil domain and C-terminal Leucine zipper domain. (B) hTRAF2, 3, 5 and 6 share the conserved TRAF domain composed of Coiled Coil TRAF-N domain and TRAF-C domain as well as RING domain and a series of Zn finger domains.hTRAF1 lacking RING domain and differs it from other TRAF members. hTRAF4 have nuclear localization region. TRAF7 has absent TRAF domain and instead of possess WD40 repeat domains.

progression in identification of TRAF family related proteins helped to elucidate the molecular mechanisms of signaling transduction emanating from TNFR superfamily and Toll/interlecukin-1receptor (Toll/IL-1R) family. TRAF2, TRAF5 and TRAF6 known as adaptor proteins that link cell surface receptors and downstream kinase cascades resulted in the activation of transcriptional factor NF-kβ activation and activator protein-1(AP-1) (Ha et al., 2009). The C-terminal side comprising of about ≈ 230 amino acids is the main signal transduction region in TRAF proteins that is conserved among all TRAF family members except TRAF7 (which does not contain TRAF homology domain) (Fig. 1) and executes the biological processes including cell proliferation, differentiation, apoptosis, inflammation and cell death (Bradley and Pober, 2001). Among all TRAF protein members, TRAF domain has been solved except TRAF7 which is controversial in respect of having no TRAF domain (Zotti et al., 2017a). The emerging evidence in last couple of years has made it easy to understand the interactions of TRAFs with their upstream regulators and downstream effectors. The membrane integrated protein receptor such as TNFR lacks the intrinsic activity at the cytoplasmic side and is believed to bind the associated proteins to transduce the signals which may be linked to immune and inflammatory responses (MacEwan, 2002). Based on the available structural information, the current understanding of structural and molecular diversity of protein- protein interacting TRAF-domain and TRAF-binding motifs together with receptor recognition has been reported (Park, 2018). Moreover, the role of TRAF proteins in diverse signaling pathways and in biological health and disease processes has widen the TRAF signaling biology (Bishop et al., 2019). Thus, TRAF members are key regulators in the immune and inflammatory systems.

2. TNF receptor associated protein 1

TNF receptor associated protein 1 has been reported to serve as an adaptor molecule that has ability to interact indirectly with the tumor necrosis factor receptor (TNFR)-associated factor 2 cytoplasmic domains and other family members of tumor necrosis factor receptor directly such as CD30, 41-BB, herpes virus entry mediator, receptor-activator of nuclear factor κ-B (RANK), CD40, Activation Inducible TNFR family member (AITR),the Epstein-Barr virus transforming protein LMP-1and BCMA which cause the nuclear factor kappa beta (NF-KB) and c-Jun N-terminal kinases (JNK) activation (Bradley and Pober, 2001). It is also known as a TNF receptor type 2 binding protein. The TNF receptor associated protein 1 is unique among the TRAF members as it lacks the RING finger domain that is found at N-terminal region for other TRAFs (Nguyen et al., 1999). Compared to other TRAF family members, cellular functions of TNF receptor associated protein 1 is poorly understood. Several studies have reported that direct interaction of TRAF1 with TRAF2 in TNFR2 signaling acts a negative regulator in T-cell. TRAF-N coiled-coil region of TRAF1 TRAF domain is critical for formation of trimer and stability of the protein in solution (Kim et al., 2016). Furthermore, studies showed that other cytoplasmic proteins such as TANK/I-TRAF (TRAF-associated NF-κB activator/TRAF interacting protein), TRIP (TRAF- interacting protein), A20, receptor interacting protein (RIP), RIP2/CARDIAK (CARD-containing interleukin (IL)-1 beta converting enzyme (ICE) associated kinase), and the caspase 8 binding protein FLIP (FLICE inhibitory protein) associates with TRAF1 (Lee et al., 1997). These cellular binding molecules modulate either positively or negatively NF-κB and JNK activation and are involved in apoptosis. Despite the consistent efforts made by researchers to elucidate the molecular mechanism of TRAF1 in different signaling pathways, the role of TRAF1 is still not well understood in these processes. The positive role for TRAF1 downstream of tumor necrosis factor receptor 2 4-IBB (also known as CD137 and TNFRSF9), GITR (glucocorticoid-induced TNFR-related), LMP1 (latent membrane proteins 1) and CD30 in company with TRAF2 has been reported recently. The suppression of TNF-α or T-cell receptor mediated apoptosis is one of the main anti-apoptotic function associated with TRAF1 (Leo et al., 2001). Recently, pro-apoptotic functions of TRAF1 has been described in neuronal cell death, which enhances the long-lasting novel therapy for stroke treatment (Lu et al., 2013). The structural importance regarding the TRAF domain of all TRAF proteins have been elucidated in signal transduction. The TRAF domain of TRAF1 was recently solved which showed both similarity and difference, which may be functionally relevant with TRAFs. To understand the exact role of TRAF1 in human diseases, TRAF deficient mouse models were utilized (Xie, 2013). In mice, TRAF1 deficiency causes atherogenesis which results the inability of monocyte recruitment to the vessel wall (Missiou et al., 2010). Therefore, TRAF1 emerged a potential treatment target for atherosclerosis. Furthermore, the crucial role of TRAF1 was shown by the serological evidence in pathogenesis (autoimmunity), confirmed by the presence of autoantibodies and serve as an inflammatory marker in Rheumatoid arthritis (RA) (Han et al., 2009) (Fig. 2).

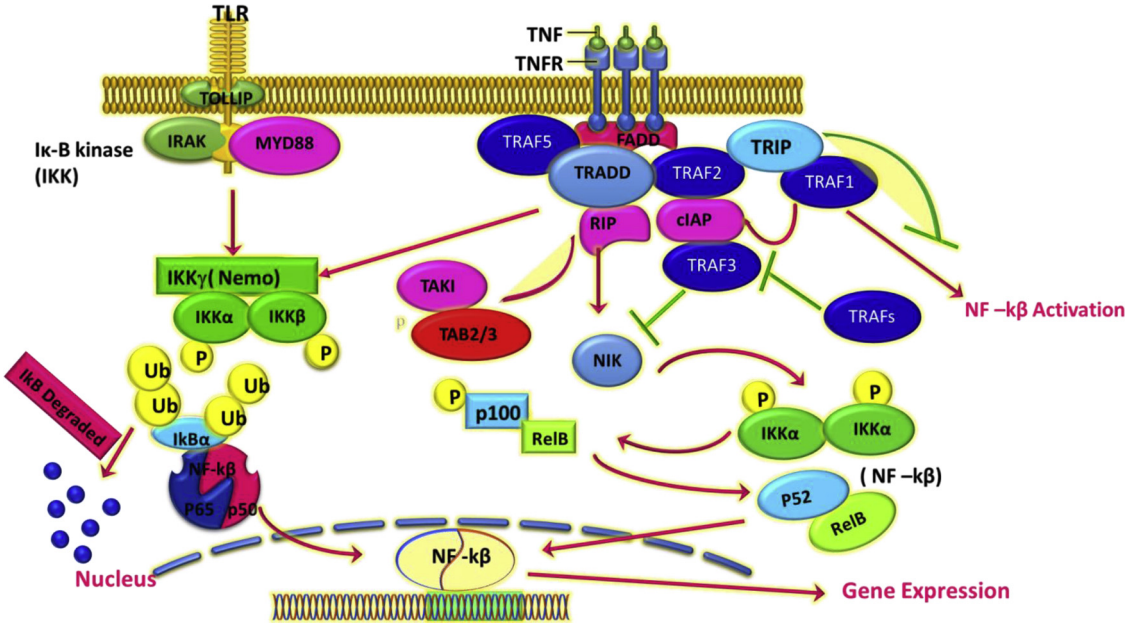

Fig. 2. TRAF 1,2,3,5 involved in NF-κB signaling pathway. TRAF1 regulates both positively and negatively activation of NF-κB pathway upon Interaction with cytoplasmic domains of TNFR. TRAF3 level of expression decreased by overexpression of TRAF1 and stabilizes the NIK.NIK is recruited upon TRADD binds to TRAF2. Moreover, MAP kinases NIK/MEKK1 and both kinases Can phosphorylate IκBα or IκBβ independently as both IKK1 and IKK2 have canonical sequences. TRAF2 an adaptor protein interacts with TRAIP(TNF interacting protein) through the C-terminal TRAF-N domain, Moreover, TRAF2 interacts with A20 zinc Protein. Both TRAIP and A20 protein prevents NF-κB activation by inhibiting the function of TRAF2. TRAF3 causes positive activation of NF-κB due to activation of IKK complex directly in classical and non classical pathway. TRAIP form complex with TRAF2 and possibly with TRAF1 causes the inhibition of NF-κB signaling pathway.

3. TNF receptor associated protein 2

Both Structurally and functionally, NF receptor associated protein 2 has been most extensively studied among TRAFs. Mutational studies have explored how distinct domains of TRAF2 interact with different proteins and lead to different signaling functions (Park et al., 1999). TRAF-N and TRAF-C sub domains independently mediate interactions with TRAF1. The function of TRAF-C domain located at C-terminal possess the sequences that interact with TNFR2 and TRADD (TNFR1-associated death domain protein), whereas N-terminal TRAF-C domain possess the sequence that mediates the interaction with RIP (receptor interacting protein) (Hsu et al., 1996). Ring fingers that follow two zinc fingers at the N-terminal region are responsible for the transcriptional factor NF-kβ activation. The structure of TRAF-N domain containing TRAF2 has shown a single alpha-helix whereas eight stranded anti-parallel strands in sandwich were found on TRAF-C TRAF domain (Zapata et al., 2001). Furthermore, TRAF2 structure revealed a mush-room shaped with a cap formed by TRAF-C and stalk formed by coiled coil domain which is important for the trimerization and stability (Zheng et al., 2010). Trimerization contributed by amino acids in TRAF domain of TRAF2 is conserved among the members of TRAF family. Crystallographic studies have shown that receptor peptide from TNFR2 interacts with only one TRAF domain leaving other two molecules without interaction in a trimer. Three residues (R393, Y395 and S467) of the TNFR2 peptide are conserved in TRAF1, 2, 3 and TRAF 5 (Ye et al., 1999). However, TRAF6 have only one conserved residue (R393).Despite having emerged as a significant molecule, no receptor interaction studies with TRAF4 have been found. There is not enough conformational change of TRAF domain in TRAF2 on interaction with receptor peptide from TNFR2, it could be possible TRAF full-length protein behaves in an unlike manner. The downstream signal trans-duction events mediated by TRAF2 particularly activation of NF-κB and activating protein-1 (AP-1) families of transcription factors, have been largely distinguished.

Bioinformatics approaches have identified the existence of three new proteins termed TEF's (TRAF domain-encompassing factors). Among the three ubiquitin specific protease, USP one isoform contains N-terminal part TRAF domain rather than the C terminal part (Ronau et al., 2016). It might be believed that recruitment of USP7 to TRAFs resulting the interference with the NF-κB activation by inhibiting I-κB degradation generated from polyubiquitination. Furthermore, tem-porary overexpression of TRAF2 and TRAF6 lead the prevention of NF-κB on the recruitment of USP7 (Xiao et al., 2012). In addition, USP7 TRAF domain expression region lacking ubiquitin-protease domain is more inhibitory than full length.

4. Role of TRAIP (TNF interacting protein) in TNF receptor associated protein 2 mediated NF-κB activation

TNF receptor associated protein 2 mediated NF-κB activation is in-hibited by number of cellular binding partners. Among them TRAIP (TNF interacting protein) is of most interesting molecule by directly binding to the TRAF2 TRAF domain resulting in the inhibition of NF-κB activation (Park et al., 2015). Recently, an *in vitro* study shows that coiled coil domain alone failed to interact with TRAF domain whereas TRAIP RINGCC domain forms the complex with TRAF domain of TRAF2 implying that RING domain is necessary for the interaction of TRAF2 TRAF domain (Bhat et al., 2018). Initially two hybrid system assays identified the TRIP protein interacting indirectly with TNFR2 and di-rectly with TRAF1 and TRAF2 resulting in the inhibition of transcrip-tional factor NF-κB activation (Besse et al., 2007). TRAIP has been in-volved in many signaling pathways such as RAP80 signaling pathway, cell cycle process or mitosis, DNA damage response, SyK-binding partner and in human diseases (Bhat and Rather, 2018). I-TRAF/TANK (TRAF-interacting protein/TRAF-associated NF-κB activator) is another binding partner act as dual inhibitor and a co inducer of TRAF2 mediated NF-κB activation (Rothe et al., 1996). Receptor interacting protein-2 (RIP2) was identified a novel binding molecule recruited to TNFR2 and CD40 receptor signaling leads to NF-κB activation and in-duced cell death (McCarthy et al., 1998). Direct interaction of RIP2 with TRAF2, TRAF3 or TRAF4 has not been reported whereas interac-tion with TRAF1, TRAF5 and TRAF6 has been reported (Bradley and

Pober, 2001). In addition, RIP2-induced NF-κB activity is prevented by the dominant negative TRAF2, suggesting RIP2 interaction with TRAF2 might occur through TRAF1. A20 is a zinc finger protein which may prevent the NF-κB activation via interaction with TRAF1/TRAF2 (Song et al., 1996). The activation of NF-κB and JNK pathways lead by two distinct kinase cascades and thus able to regulate by TRAF2 (Fig. 5).

5. TNF receptor associated protein 3

Initially TNF receptor associated protein 3 was described as an immune molecule which interacted with the cytoplasmic tails of CD40 (Hildebrand et al., 2011). It is a multifunctional adaptor protein in both innate and acquired immune systems that has its role in RIG-I-like receptor (RLR) and Toll-like receptor (TLR) signaling pathway in mammals (Takeuchi and Akira, 2010). A variety of immune cells such as dendritic cells, B cells, macrophages and monocytes, endothelial cells, smooth muscle cells and fibroblasts express CD40 (Ma and Clark, 2009). Antibody secretion mediated by CD40 is inhibited by overexpression of TRAF3 and this consequence was influenced on an intact TRAF binding site on CD40. TRAF3, a E3 ubiquitin ligase which interacted with adapter inducing IFN-β (TRIF) containing TIR domain and myeloid differentiation primary response gene 88 (MyD88) leads to the production of type-I interferons and inflammatory cytokines (Häcker et al., 2011). In mammals, the non-canonical NF-κB signaling functions as negative regulator by constantly lead the degradation NF-κB-inducing kinase (NIK). In birds, significantly increased IFN-β promoter activity by pigeon TRAF3 (piTRAF3) resulted the potential function in antiviral defense response (Zarnegar et al., 2008). Additionally, Chicken TRAF3 involved in defending against poly (I:C) and poly dA-dT challenges demonstrated by TRAF3 data (Yang et al., 2015). TRAF3 expression has also been shown in platelets where it plays a negative role in regulating platelet activation (Zhang et al., 2017). Experiments of TRAF3 null mice have shown that TRAF3 is not needed in CD40 signaling in B cells. TRAF3 deficient mice are diminished in all lineages of peripheral leucocytes and die soon after birth (Xu et al., 1996).

TNF receptor associated protein 3 was identified independently as an interacting protein with Epstein- Barr virus latent membrane protein, LMP1, and is known to interact with other TNF receptor family members. Infected B-lymphocytes are proliferated by Epstein- Barr virus through expression of nuclear proteins and the integral membrane proteins, LMP1, an constitutively active TNF receptor. TRAF3, also TRAF1, 2, and 5 binds the C-terminally cytoplasmic domain site and mediates both EBV induced B cell proliferation and NF-κB activation (Izumi et al., 1999). The recruitment of TRAF3 in a ligand dependent manner to the lymphotoxin-β, receptor (LTβR) can have an inhibitory effect on NF-κB activation through LTβR. The TRAF3 also act as a crucial component in the induction of cell death by LT-β (Lymphotoxin-β) (VanArsdale et al., 1997) and inhibited cell death signaling by TRAF3 dominant mutant through lymphotoxin but not TNF (Force et al., 1997).

6. TNF receptor associated protein 4

TRAF4 was recognized by differential screening of a cDNA library in breast carcinoma overexpressed as a gene (Tomasetto et al., 1995; Regnier et al., 1995). It has been shown that TRAF4 predominantly localizes in the nucleus and has not shown to regulate signaling through cell surface receptors. However, expression of TRAF4 gene is not restricted to breast cancer and increased to a variety of different carcinoma (Rhodes et al., 2004; Camilleri-Broët et al., 2007). TRAF4 is one of the most conserved member of TRAF family during evolution (Kedinger and Rio, 2007). Worm TRAF protein shares a higher homology with human TRAF4 than other human proteins (Preiss et al., 2001). Moreover, among the three fly TRAF proteins, one TRAF protein dTRAF shares the highest homology with TRAF4 (Tomasetto et al., 1995). Weak interactions between TRAF4 and LTβR and p75 nerve growth factor receptor revealed by *in vitro* binding assays, but lacking with TNFR1, TNFR2, Fas or CD40 (Grech et al., 2001). Approximately one-third of the homozygous mutants are lethal at the embryonic stage due to TRAF4 deficiency. Moreover, all surviving animals exhibited multiple defects including gross trachea, neural tube axial skeleton in the central nervous system (Krajewska et al., 1998; Shiels et al., 2000). TRAF4 has been reported to be involved in initiation and progression of many types of cancer such as breast, lung, ovary, colon, and prostate cancer, suggesting TRAF4 preliminary target for cancer treatment (Régnier et al., 2002; Li et al., 2013). TRAF4 might use different interacting mode for binding with other different receptors as it lacks conserved hot spots for interaction has revealed by the sequence comparison of other TRAF family members. Recently, TGF-β (Transforming growth factor-β) signaling activation was shown by TRAF4 and transduce both SMAD and non-SMAD pathways to develop breast cancer (Zhang et al., 2013). Increased overexpression of TRAF4 in ASMSCs impaired LPS-induced autophagy, potentially prevented the phosphorylation of Beclin-1 (Xie et al., 2016).

7. TNF receptor associated protein 5

TNF receptor associated protein 5 was initially identified as a protein that potentially interacts with LTβR (Lymphotoxin-β receptor) (Nakano et al., 1996) and CD40 (Ishida et al., 1996), and is engaged in NF-κB activation by CD27 (Akiba et al., 1998a) and CD30 (Aizawa et al., 1997). TRAF5 is an important regulator emerging for many immune cell functions. Full length TRAF5 overexpression activated the transcriptional activator NF-κB, but truncated form lacking Zinc binding region is unable to activate NF-κB (Leo et al., 1999). TRAF5 interacts with CD40 indirectly, involving hetero-oligomerization with TRAF3 (Shen et al., 2013). TRAF5 and TRAF3 share a common ancestral gene and therefore most homologous (Aizawa et al., 1997). Human TRAF5 consists of 557 amino acids and 558 amino acids in mice and is located at chromosome 1.TRAF5 is composed of a C-terminally binding domain(TRAF-C), followed that coiled coil, leucine zipper domain (TRAF-N), five zinc finger domain and an N-terminal RING finger domain (Pullen et al., 1998). Interaction of TRAF5 with TRAF3 results the formation of homotypic multimers or heterotypic multimers, which has shown to be biologically important for recruitment of TRAF5 to various receptors (Ishida et al., 1996; Akiba et al., 1998b). Although, TRAF5 and TRAF3 are structurally similar, but functionally TRAF5 is most similar to TRAF2. On TNF receptors both TRAF5 and TRAF2 share an overlapping binding site and are putative positive regulator of a number members of TNFR superfamily (He et al., 2004).

8. TNF receptor associated protein 6

TNF receptor associated protein 6 was recognized as a signal transducer for IL-1 (Cao et al., 1996). Studies showed that activation of NF-κB caused by overexpression of TRAF6, and NF-κB activation is prevented by negative mutant of TRAF6 by IL-1 but not TNF. Overexpressed TRAF6 also activates JNK and p38 (Song et al., 1997). TRAF6 has unique function because it possesses the TRAF-C domain that have distinct specificity for receptors and downstream signaling proteins. TRAF6 is involved in many biological processes which include the myeloid differentiation primary response gene 88 (MyD88) signaling network of the innate immune system and osteoclast formation, lymph node organogenesis and RANK ligand (RANKL)-dependent signaling (Naito et al., 1999), and the development of hair follicles and sebaceous glands (Naito et al., 2002). TRAF6 possess a ubiquitin ligase activity and induces the activation by Toll-like receptor, TNF-alpha receptor and IL-1 receptor, resulting in the ubiquitin dependent degradation of other proteins such as IKKs. TRAF6 ligase activity is not essential for the IL-1dependent formation of k63-Ub chains, TAK1 activation, or IL-8 production in human cells because K63 –Ub chains generates by Pellino1 and Pellino2 are required for signaling in cells expressing E3

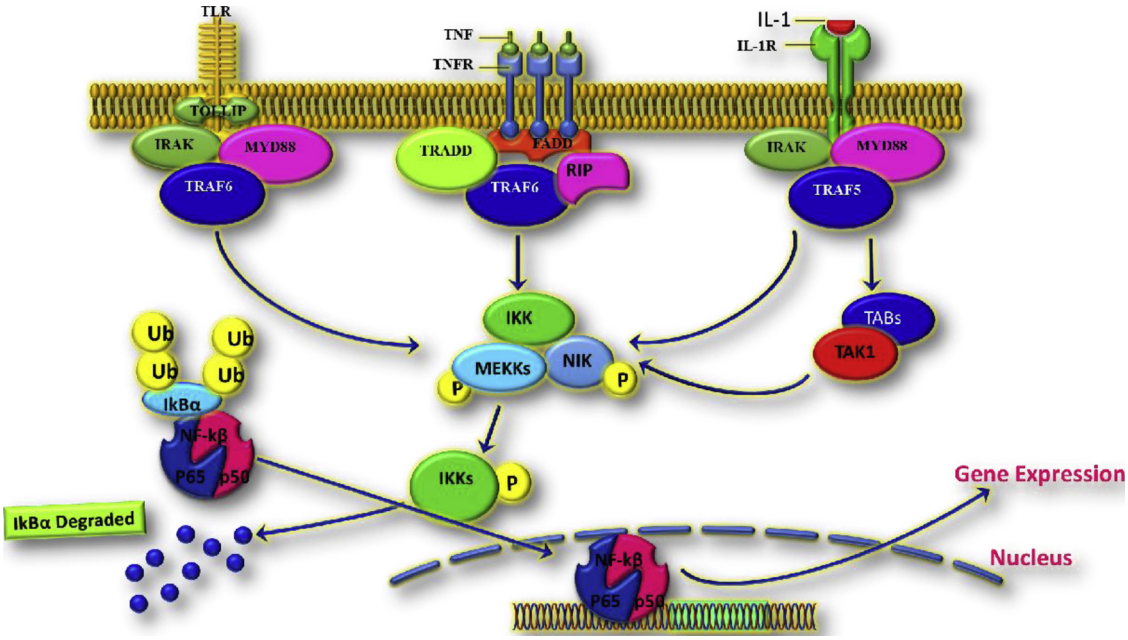

Fig. 3. TRAF6 an E3 Ubiquitin ligase is activated by the Toll-Like receptor, TNF-alpha receptor and IL-1 receptor and activated TRAF6 could induce the ubiquitin mediated degradation of other proteins such as IKKs. So TRAF6 acts a regulator of signaling in cell.

ligase-inactive TRAF6 mutants (Strickson et al., 2017). So it behaves as a switch of signaling in cell. Coiled-coil domain is critical for TRAF6's processivity and also mediates the TRAF6 oligomerization enable efficient polyubiquitin chain assembly (Hu et al., 2017) (Fig. 3).

TRAF6 is unique in that it recognizes completely distinct binding sites other than TRAFs 1, 2, 3 on the members of the TNFR superfamily such as CD40 and RANL. In membrane proximal region sequence ^{231}QEPQEINF that has been mapped where TRAF6 binds (Nakano et al., 1996). TRAF6 null mice associates predominantly the defective bone formation. Impaired osteoclast formation occurred due to severe osteopetrosis with defects in bone remodeling and tooth eruption found in deficient mice of TRAF6 and die at early age (Lomaga et al., 1999). It has been also defined the role of TRAF6 in IL-17 signal transduction using embryonic fibroblast from TRAF6 knockout mice. In TRAF6 deficient mice, IL-17 fails to activate the NF-κB and JNK, eradicating IL17 induced IL-6 and intracellular adhesion molecule 1 expression (Schwandner et al., 2000).

9. TNF receptor associated protein 7

TNF receptor associated protein 7 recognized as seventh member of TRAF family, engaged in signal transduction pathways lead either activation or inhibition of NF-κB. The N-terminal domain possess Ubiquitin ligase RING finger(125–160 a. a), followed by an zinc finger motif (221–287a.a). TRAF 7 contains seven WD40 repeats at the carboxy terminal end instead of homology TRAF domain (Bouwmeester et al., 2004; Xu et al., 2004). TRAF7 has been identified for its association with MEKK3.the interaction of TRAF7 with MEKK3 is mediated by WD40 repeats at the carboxy terminal region, while other TRAF members interact with other signaling molecules through TRAF domain including protein kinases (Bouwmeester et al., 2004). The signal transduction pathways in which activation of JNK and p38 MAP kinases occurred upon cooperative interaction of TRAF7 and MEKK3 results TNFα stimulation (Bouwmeester et al., 2004; Xu et al., 2004; Wang et al., 2013). Some cellular stress pathways are regulated by TRAF7 as well as few unusual ubiquitination events and differentiation of muscle tissue (Tsikitis et al., 2010). Lys28 –linked ubiquitination of p53 promotes by the TRAF7 (Wang et al., 2013). From last several years, the increasing evidence of its involvement in the genesis and progression of several human cancers placing it as novel tumor suppression protein (Zotti et al., 2017b). Specifically, TRAF7 is mutated in nearly 25% meningiomas and significantly, however, at a lower rate in human mesotheliomas.Lys29 –linked ubiquitination of NF-κB essential modulator (NEMO) and p65 promoted by TRAF7 (Zotti et al., 2011) (Fig. 4).

10. TRAFs associated diseases

The understanding of TRAFs role in human pathogenesis were revealed by the TRAF deficient mouse models. They have regulatory role in cell development, survival and activation of various cell types. Due to their aberrant functions, it would be expected to contribute different possible diseases. Some disease associated with TRAFs are shown in Table 1.

11. B-cell malignancies

There is consistent evidence of TRAF3, TRAF2, TRAF1 relevance with B-cell malignancies. Multiple myeloma is caused by the deletion and mutation of TRAF3 (Annunziata et al., 2007; Keats et al., 2007). Waldonstroms macroglonumeria (Braggio et al., 2009) Hodgkin lymphomas (Otto et al., 2012) and other number of non-Hodgkin lymphomas such as splenic marginal zone lymphomas, B-cell chronic lymphocytic leukemia and mantle cell lymphoma (Rossi et al., 2011; Nagel et al., 2009). In multiple myeloma, an inactivating mutation of TRAF2 have been identified (Demchenko et al., 2010) and diffuse large B-cell lymphomas (Compagno et al., 2009). Increased Risk of Multiple myeloma is also associated with the single nucleotide polymorphisms of TRAF3 (Du et al., 2011). However, TRAF1 expression is elevated in both Hodgkin lymphomasand non-Hodgkin lymphomas, largely B-cell chronic lymphocytic leukemia and mediastinal large B-cell lymphoma (Savage et al., 2003; Munzert et al., 2002; Zapata et al., 2000).

12. Carcinomas

Carcinomas is caused due to the overexpression and gene amplication of the TRAF4 and TRAF6 in humans. Breast and lung carcinomas is associated with overexpression of TRAF4 (Bièche et al., 1996). The sub cellular localization of TRAF4 is mainly in cytoplasmic in large number

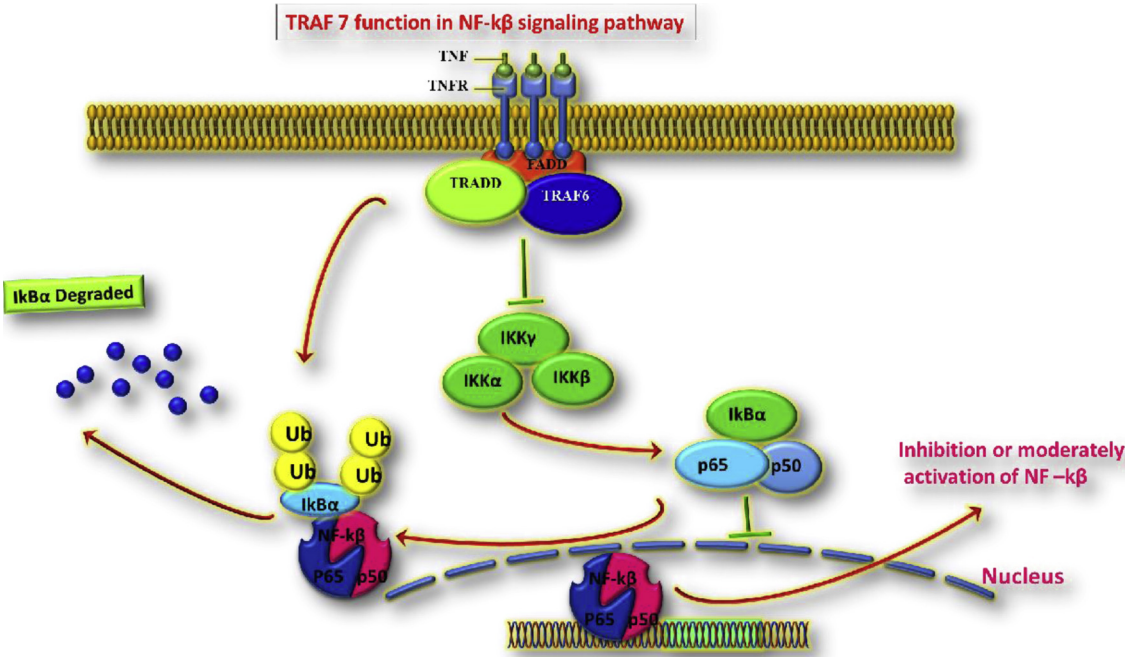

Fig. 4. TRAF7 involved in NF-κB signaling pathway.TRAF7 prevented the NF-κB signaling and induces the apoptosis via ubiquitin degradation of Lys29 in IKKγ, resulting the inhibition of NF-κB signaling pathway.

of cases and overexpression is limited to cancer cells. The increased TRAF4 gene copy number is one major mechanism responsible for TRAF4 protein overexpression in human cancers. Interestingly, p53 family of transcription factors, carrying p63, p73 and p53 targets the TRAF4 gene in squamous cell carcinoma of the head and neck (SCCHN).TRAF4 overexpression induces apoptosis in (SCCHN) and suppresses colony formation (Sax and El-Deiry, 2003; Rozan and El-Deiry, 2014; Gu et al., 2007). As a result, TRAF4 overexpression has different outcomes from different carcinomas. TRAF6 Overexpression and gene amplication is associated with lung cancer and osteosarcoma cells (Zhong et al., 2013). In human lung cancer and osteocarcinoma, TRAF4 down regulation suppresses NF-κB activation, cell survival and proliferation, and tumor formation and invasion. Therefore it is concluded that TRAF6 overexpression may promote tumorigenesis and invasion of lung cancer and osteocarcinoma cells (Zucchelli et al., 2011).

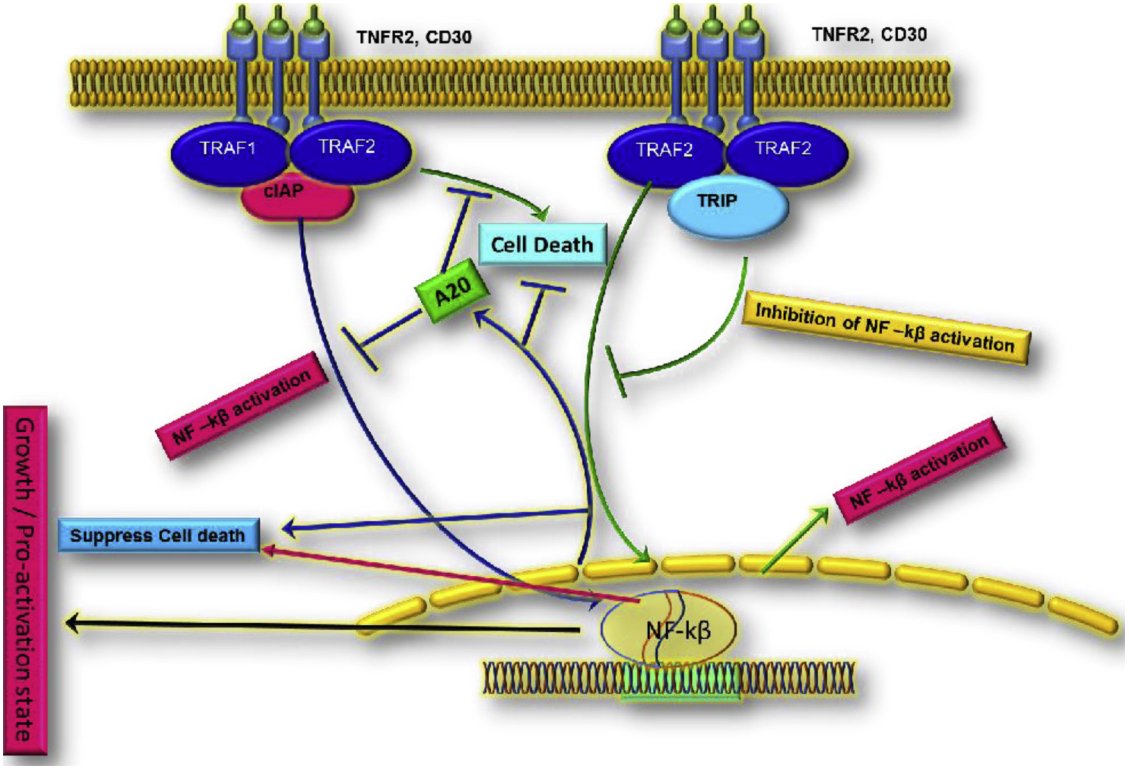

Fig. 5. A model shows inhibiting activity of TRIP, c-IAP for TRAF1 and TRAF2 mediated NF-kβ signaling pathway leading to either cell activation or cell death.

Table 1
TNF receptor associated factors (TRAPs's) in human disease.

Diseases	TRAFs variation at genetic level	Reference
B cell malignancie		
Multiple myeloma	Deletion or inactivating mutations of TRAF3, TRAF2 SNPs of TRAF3	(Annunziata et al., 2007; Keats et al., 2007; Demchenko et al., 2010)
Splenic marginal zone lymphoma	Deletion or inactivating mutations of TRAF3	(Rossi et al., 2011)
B cell chronic lymphocytic leukemia	Deletion or inactivating mutations of TRAF3	(Nagel et al., 2009)
Mantle cell lymphoma	Deletion or inactivating mutations of TRAF3	(Nagel et al., 2009)
Waldenström's macroglonuria	Deletion or inactivating mutations of TRAF3	(Braggio et al., 2009)
Hodgkin lymphoma	Deletion of TRAF3	(Otto et al., 2012)
Diffuse large B cell lymphoma	Inactivating mutations of TRAF2, TRAF5	(Compagno et al., 2009)
Non-Hodgkin lymphoma	SNPs of TRAF1	(Rossi et al., 2011)
Carcinomas		
Breast cancer	Amplifying of TRAF4	(Bièche et al., 1996)
Lung cancer	Amplifying of TRAF4, TRAF6	(Zucchelli et al., 2011)
Osteosarcoma	Amplifying of TRAF6	(Zucchelli et al., 2011)
Autoimmune disease		
Systemic lupus erythematosus	SNPs of TRAF6, TRAF1/C5	(Lee and Song, 2012; Rajabi et al., 2012)
Rheumatoid arthritis	SNPs of TRAF5, TRAF6, TRAF1/C5	(Zucchelli et al., 2010)
Immunodeficiencies		
HSV-encephalitis	Inactivating mutations of TRAF3	(Pérez de Diego et al., 2010)
Other		
Hypohidrotic ectodermal dysplasia	Inactivating mutations of TRAF6	(Wisniewski and Trzeciak, 2012)

13. Neurodegenerative diseases

TRAF6 involved in the pathogenic aggregation of mutant proteins in neurodegenerative diseases such as Parkinson's disease and Huntington disease and possess the E3 ligase activity. The misfolded mutant DJ-1, a SYN and N-HTT, involved in the pathogenesis of the Parkinson's disease and Huntington disease has shown to be interacted with TRAF6. In contrast to K63-linked polyubiquitination, TRAF6 promotes atypical ubiquitination of DJ-1, a SYN and N-HTT with K6, K27, and K29 linkage formation, therefore trigger formation of mutant DJ-1, a SYN and N-HTT in neurodegenerative diseases (Zucchelli et al., 2010; Jin et al., 2008).

14. Autoimmune disease

Autoimmune diseases such as Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are linked to Single nucleotide polymorphisms (SNPs) in TRAFs. Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are associated with SNPs of TRAF6 (Lee and Song, 2012). Likewise, SNPs atTRAF1/C5 locus are cooperated with both SLE and RA (Zucchelli et al., 2010). In SLE patients, decreased expression of TRAF2 has been detected in peripheral blood mononuclear cells (Rajabi et al., 2012). Further studies needed to done to know their roles in SLE and RA susceptibility.

15. Immunodeficiencies

TRAF3 autosomal dominant mutation is exhibited in young adults and herpes simplex virus-1 (HSV-1) encephalitis which is devastating infection in CNS and is peak in childhood (Pérez de Diego et al., 2010). The TRAF3 mutant allele is loss-of-expression, loss-of-function, and dominant-negative and associated with impaired, upon stimulation of both TNFRs and receptors that lead to IFN production (Zhong et al., 2013).

16. Hypohidrotic ectodermal dysplasia

Patients with Hypohidrotic ectodermal dysplasia (HED) which is caused by the TRAF6 heterozygous mutation has been reported (Wisniewski and Trzeciak, 2012). TRAF6 mutant protein forms complex with TAK1 and TAB2, but is unable to form complex with receptor XEDAR (X-linked ectodermal dysplasia receptor). Moreover, TRAF6 mutant protein prevents the interaction between wild type TRAF6 and XEDAR and inhibited the XEDAR mediated NF-kβ activation (Fujikawa et al., 2013).

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Declaration of Competing Interest

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

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