DEATH RECEPTOR MEDIATED CELLULAR APOPTOSIS: A MECHANISM BASED REVIEW

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Abstract:

The term **"**apoptosis" represents spontaneous single cell death, with specific biochemical and morphological features. Various cellular stresses can initiate apoptosis by the activation of receptors such as Tumor Necrosis Factor Receptor (TNFR), Fas receptor etc. Various ligands that are associated with these receptors include growth factors, anti cancer agents and some other chemotherapeutic agents, ionizing radiations, Fas ligand etc. Association of these ligands with their respective receptors may relay the signals to the catalytic site to release the second messengers there by initiate apoptosis and cellular death can triggers. Cellular apoptosis and cellular death may also occur as a defense mechanism such as in immune reactions or when cells are damaged by disease or noxious agents. Fas-associated protein with death domain not only contains a death domain but also contain a Death Effector Domain (DED) that binds to an analogous domain repeated in cycle within the zymogen form of Caspase-8. Fas ligand binds with Fas-associated protein with death domain (FADDs). The complex of Fas receptor, fas-associated protein with death domain and Caspase-8 are called the Death Inducing Signaling Complex (DISC). Activation of Caspase-8 in turn activates downstream caspases committing the cell to apoptosis. In this review, we have tried to summarize the molecular basis of cellular apoptosis and cellular death via different signal transduction pathways.

Key words: Death receptor, cellular apoptosis, TNF receptor, death ligands, Signal transduction

Introduction:

In the cell living cycle of every cell growth and death are naturally occurring phenomenon for all multicellular organisms; cell death can occur by cell injury or cell necrosis called apoptosis. Apoptosis is the process of cell signaling auto-destruction often called "programmed cell death". It is an extremely regulated cell signaling process characterized by morphological and biochemical changes caused by activation of a family of proteases called caspases. These are Programmed cell death, also called apoptosis. This is clearly distinct from necrosis, the result of unintended cell death or apoptosis. It is a *Greek* word the term 'apoptosis' means falling off leaves from trees. It was first described in 1972 by Kerr and co-workers Wyllie, and Currie[1] to describe a morphologically distinct form of cell death.[2, 3, 4] They also occur as a defense mechanism such as in immune reactions or when cells are damaged by disease or noxious agents.[5] The apoptosis mode of cell death is an

active and defined process which plays an important role in the development of multicellular organisms and in the regulation and maintenance of the cell populations in tissues upon physiological and pathological conditions.[6]

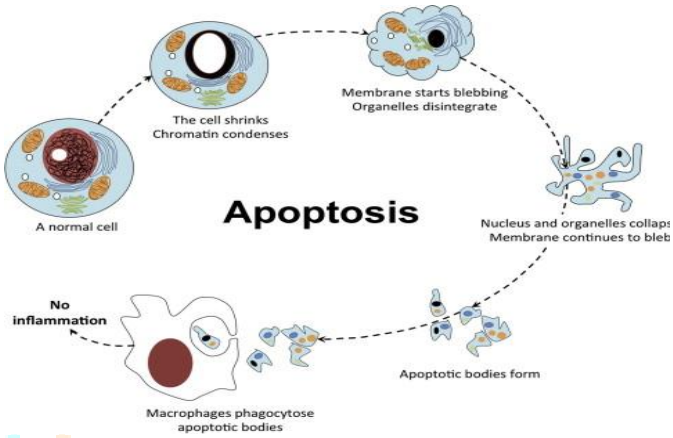

Fig- 1. Process of Cellular apoptosis

There are different stimuli that induce a cell to undergo apoptosis in absence of survival factors, or in case of irreparable internal damage or in case of incompatible signals driving the cell cycle a cell initiates the cell death program. A passive response of the cell to "irregular problems" in its surroundings or in its own cell life-cycle but they have evolved a mechanism that enables the organism actively to direct individual cells to self-destruct. [7]. It can be triggered by a number of factors including UV- or γ-irradiation, chemotherapeutic drugs or signaling by death receptors. [8] Death receptors have been an attractive pharmacological target even before their characterization at the molecular level and clinical successes achieved by modulating the activity of death receptors.[9]

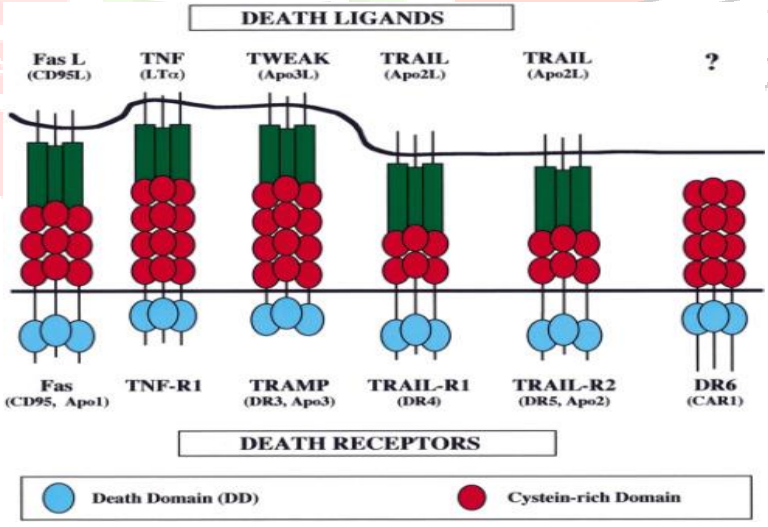

Fig- 2. Architecture of death receptors with their ligands

- **SUB-TYPES OF DEATH RECEPTORS**

Fas receptor (FASR)

The FAS receptor (FasR) is also known as apoptosis antigen-1 is a protein that is encoded by the *FAS* gene in humans. [10, 11] The Fas receptor is a death receptor on the surface of cells that leads to programmed cell death or apoptosis. It is one of two apoptosis pathways and the other being the mitochondrial pathway. Fas Receptor is located on Chromosomes 10 and 19 in Humans and Animals respectively. Similar sequences related by augmentation are found in most mammals.[12] It is a transmembrane receptor expressed in particular in brain, heart, kidney, liver, pancreas, thymus and lymphoid tissues. It belongs to the death receptor family, a subgroup of the Tumors Necrosis Factor (TNF) or Nerve Growth Factor (NGF) receptor superfamily [13, 14, 15] and acts as the target of cell death-inducing antibodies. [15] Fas receptors are currently comprising 29 receptors that are mirrored by only 19 ligands, representing the related TNF ligand superfamily. This already indicates that a single ligand might be capable to bind to more than one receptor and that there still exist orphan receptors.[16] Activation of Cluster of Differential 95 (CD95) associated intracellular signaling pathways is not a simple consequence of ligand binding but is the result of a complex interplay of various molecular mechanisms that eventually determine the strength and quality of the CD95 response.[17] The Fas receptor was identified in 1989 as a target for antibodies that induce apoptosis in various human cell lines.[18] Human Fas consists of 325 amino acid with a signal sequence at the N-terminus and a membrane-spanning region in the middle of the molecule, indicating that Fas is a type-I membrane molecule. Its structure showed homology to the TNF and NGF receptor family. [19]

The Fas Pathway

Fas Ligand is a homotrimeric membrane-molecule each Fas ligand is bound with three Fas receptor molecules on the surface of the target cell. The clustering of the receptors death domains which then engage the cytosolic adapter protein. Fas ligand binds with Fas-associated protein with death domain (FAS-ASSOCIATED PROTEIN WITH DEATH DOMAIN). Fas-associated protein with death domain not only contains a death domain but also contain a Death Effector Domain (DED) that binds to an analogous domain repeated in a cycle within the zymogen form of Caspase-8. The complex of Fas receptor, FAS-ASSOCIATED PROTEIN WITH DEATH DOMAIN and Caspase-8 is called the Death-Inducing Signaling Complex (DISC). Active Caspase-8 then activates downstream caspases committing the cell to apoptosis.[20] The Fas system plays a dual role in tumor development and metastasis. The apoptotic signal of Fas is executed upon Trans binding of homotrimeric Fas ligand. Trimerization of Fas receptors and their intracellular death domain creates a docking site for a Fas-associated protein with death domain, which is required for induction of the extrinsic caspases- 8 dependent apoptotic pathways [21]. Furthermore, this pathway is only induced by membrane-bound Fas ligand [22], possibly mediated by receptor capping into focal points within the cell membrane. This could occur by a two-step process [23] Fas palmitoylation is required for Fas-induced cell death [24] Whereas the canonical death pathway is activated by Fas in so-called type-I cells to mediate apoptosis, for apoptosis to occur in type-II cells the pathway requires simplification by the intrinsic mitochondrial pathway [25,26]. Thus the extrinsic and intrinsic apoptotic pathways are interconnected in type-II cells, with partial activation of caspase-8 being sufficient to cleave Bid and trigger the amplification loop. However, Fas is also capable of promoting a non-apoptotic response following Fas ligand binding in situations where the apoptotic pathway is blocked. [27].

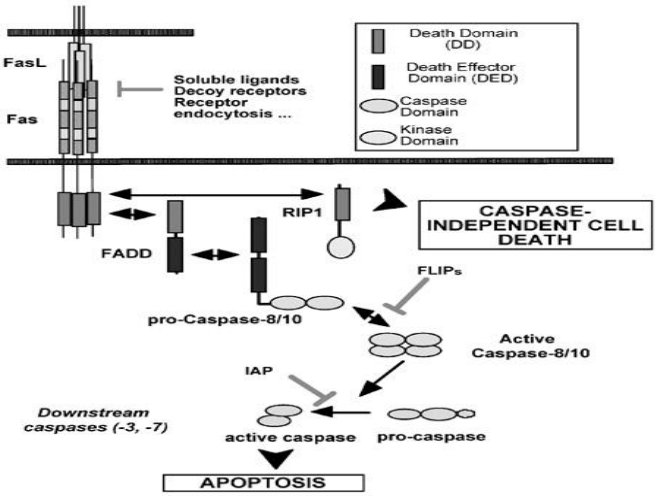

Fig- 3: Diagrammatic illustration of 'Fas' signaling pathways for cellular apoptosis.

Tumor Necrosis Factor Receptor (TNFR)

Members of the tumor necrosis factor receptor family initiate a signal that leads to programmed cell death or promotes cell survival and proliferation. [28, 29] Death Receptors belonging to the Tumor Necrosis Factor Receptor gene superfamily. [30] Members of that TNFR family are diverse in primary structure but all of them consist of cysteine-rich extracellular subdomains [31] that thought to adopt generally similar tertiary folds.[32] Nevertheless, it is the unique structural features of individual family members that allow them to recognize their ligands with specificity and, in most cases, exclusivity. [31] Additionally the death receptors contain a homologous cytoplasmic sequence termed the "death domain". Adapter-molecules like fas-associated protein with death domain, type 1-associated death domain themselves contain death domains so that they can interact with the death receptors and transmit the apoptotic signal to the death-machinery. [33]

TNF-R1 AND TNF-α

The TNF-receptor signaling system consists of two distinct receptors TNF-R1 and TNF-R2, and three ligands, the membrane-bound TNF-α, the soluble lymphocyte-derived cytokine[34] However, only TNF-R1 is considered a canonical death receptor as TNR-R2 does not possess an intracellular death domain. TNF-R1 is universally expressed at constitutively low levels and controlled by a noninducible promoter. Although TNF-R1 and TNF-R2 interact with both forms of TNF-α, as well as with TNF-R1 appears to be largely responsible for TNF signaling in most cell types.[35,36] Tumor necrosis factor-α (TNF-α) plays a key role in inflammation and immunity, as well as in proliferation and differentiation of many different target cells.[37] TNF-α is mainly produced by macrophages, monocytes, and T cells in response to infection and inflammatory conditions, but also by other cell types, such as B cells, fibroblasts, and hepatocytes. Both soluble and membrane-bound TNF-α are biologically active, and while the soluble form acts as an effector molecule at a distance from the producer cell, the membrane-bound form likely has a specific role in localized TNF- α responses.

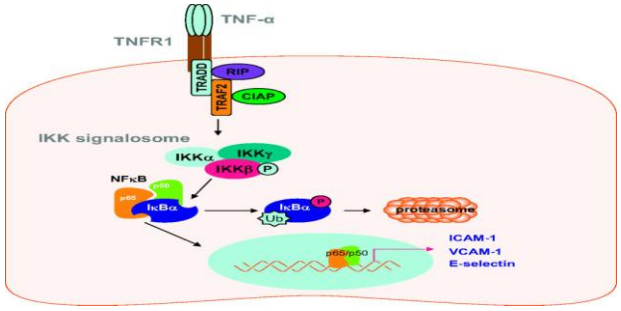

Fig- 5. TNF-receptor signaling system

The widespread expression of TNFR1 and its pleiotropic nature of signaling. The physiological roles of the TNF signaling system are numerous. TNFR1 plays a major role in maintaining immune homeostasis by promoting apoptosis, cell survival, differentiation, and inflammation. [38,39] In a crucial role of TNFR1 in modulating immune responses, dysregulation of TNFR1 signaling is thought to cause several autoimmune diseases.[40]. Dysregulation of TNF also causes auto-immune diseases such as psoriasis, autoimmune arthritis, multiple sclerosis, and diabetes mellitus. The majority of these diseases are thought to relate to the ability of TNF to promote expression of pro-inflammatory genes via the (Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells) NF-κB signaling pathway. [41] The pro-inflammatory nature of TNF signaling is also thought to contribute to cancer. The majority of that TNF has the ability to promote tumor development, proliferation, invasion, angiogenesis, and metastasis [42] TNFR1 has also to be involved in the neuronal activity in the brain, beyond mediating inflammation. [43] TNFR1 is activated by binding of lymph toxin - α (LTα). A Complex-I induces survival and inflammatory responses by activating the MAPK and JNK pathways. Complex-I further promotes survival and proliferation by activating NF-κB via the pro-survival kinase (Transforming Growth Factor Beta-Activated Kinase-1)TAK-1 [44] Activation of NF-κB also requires ubiquitination of (Receptor-interacting protein) RIP-1 by the ubiquity ligases cIAP1 and 2 [45,46]. However, upon receptor internalization, a Fas-associated protein with death domain mediated death signaling can also be triggered [47, 48] Furthermore, dissociation of type 1-associated death domain can be regulated by a conformational change in the receptor or by ubiquitination of RIP-1. The activity of complex-II As regulated by the caspase-8 inhibitor cellular FLICE inhibitory protein (cFLIP) whereas that of Complex-II Bisregulated by the levels of cIAP1 and 2 [49]. One hypothesis as TNFR1/ DR3 mediate a non-apoptotic response when DISC formation occurs, whereas apoptosis mediated by DISC formation is stimulated by Fas or DR4/5, is because the latter receptors trigger a global cellular response, whereas DISC formation following TNFR1 internalization allows for compartmentalization, restricting caspases activity. Depending on the context, TNFR1-mediated DISC assembly can also alternatively promote cell survival, proliferation or differentiation as described above. The cellular outcome critically depends on the constituents of DISC and on the subcellular localization of activated TNFR1 [137]. Death Receptor 3 As the receptor with highest homologytoTNFR1, DR3 signaling pathways are similarly relayed through type 1-associated death domain, RIP, and TRAF2 [50]. Although DR3 is capable of executing an apoptotic response, promoting apoptosis among thymocyte [51], it plays an important modulatory role in immune responses through the formation of Complex I, by activating the MAPK, JNK, and NF-κB signaling pathways following binding of its ligand a TNF-like cytokine Ligand (TL1A)

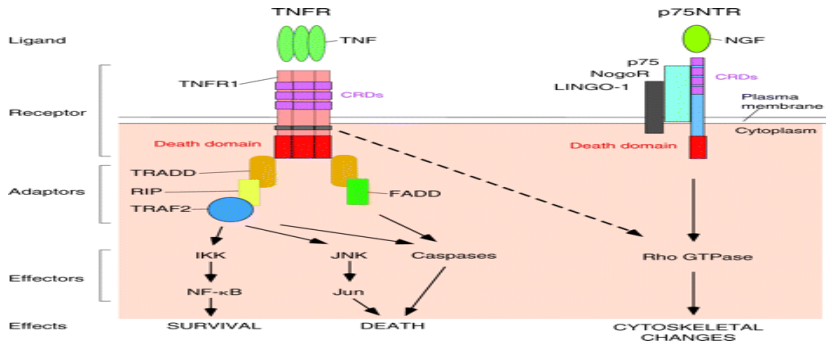

Fig- 6. **Diagrammatic expression of different catalytic activities via Tumor Necrosis Factor Receptor Pathways**

Death receptor 3 (DR3)

Death receptor 3 also known as tumor necrosis factor receptor superfamily member 25 is a cell surface receptor of the tumor necrosis factor receptor superfamily which mediates apoptotic signaling and differentiation [52,53] The signaling from death receptor 3 is similar to TNFR-1. It uses type 1-associated death domain and Fas-associated protein with death domain as adapter molecules, and caspase-8 is the apical caspase activated by the receptor complex.[54] DR3 was identified more than 5 years ago by several groups as a death receptor displaying the highest homologies with TNF-R1, with predominant expression in lymphocytes. The ligand of DR3 is TL1A, a recently discovered member of the TNF ligand family. Generation of DR3-deficient mice revealed a role of this receptor in negative selection and anti-CD3-induced cell death of T-cells [55] So far, it appears that DR3 elicits the same cellular pathways as TNF-R1, using the same set of receptor-associated proteins. Thus DR3 induces apoptosis by type 1-associated death domain mediated recruitment of Fas-associated protein with death domain and caspase-8 and triggers NF-κB activation via RIP and TRAF2. The non-redundant functions of DR3 and TNF-R1 are therefore most likely to be related to the different expression patterns of these receptors.

Signaling by DR3

DR3 are shows close sequence similarity to TNFR1 [56] upon overexpression, DR3 triggers responses that resemble those of TNFR1, the NF-κB activation, and apoptosis. Like TNFR1, DR3 activates NF-κB through type 1-associated death domain, TRAF2, and RIP and apoptosis through type 1-associated death domain, a Fas-associated protein with death domain, and caspase-8. DR3 binds to Apo3L, which is related most closely to TNF [57], Apo3L activates NF-κB through type 1-associated death domain, TRAF2, RIP, and NIK and triggers apoptosis through type 1-associated death domain and Fas-associated protein with death domain, consistent with signaling through DR3. Thus, with respect to the regulation of NF-κB and apoptosis, Apo3L closely resembles TNF. There are extraordinary differences, however, in the expression of these ligands and receptors. TNF expression occurs mainly in activated macrophages and lymphocytes [58], whereas Apo3L messenger RNA is expressed constitutively in many tissues [56] Conversely, TNFR1 is expressed ubiquitously, whereas DR3 transcripts are present mainly in spleen, thymus, and peripheral blood and are induced by activation in T cells [59] Hence, despite overlapping signaling mechanisms, Apo3L-DR3 and TNF-TNFR1 interactions probably have distinct biological roles.

DR4 and DR5

The two DRs DR4 and DR5 belong to the same homology clade as Fas and promote apoptosis via a similar pathway to Fas.In humans, the TNF-related apoptosis-inducing ligand interacts with DR4 and DR5, which in turn directly interact with Fas-associated protein with death domain and cause DISC assembly. Hence,

activation of DR4 or DR5 can mediate both the extrinsic and intrinsic apoptotic signaling pathways. Signaling through DR4 and DR5 has been suggested to modulate immune responses to avoid reaction to self-reactive antigens and kill virally infected cells [60,61]. Furthermore, mDR5 and TRAIL are known to suppress tumor growth and metastasis by specifically promoting apoptosis among cancer cells while sparing non-transformed cells, However, it has indicated that DR4 and DR5 also have the capacity to activate non-apoptotic signaling pathways via the MAPK, JNK, and NF-κB pathways [62,63]. TRAIL also interacts with the two so-called decoy-receptors DcR1 and DcR2, which are both incapable of transmitting an apoptotic signal. Whereas DcR1 does not possess a cytoplasm or Transmembrane domain and is instead attached to the membrane via a glycosylphosphatidylinositol-anchor, DcR2 has a truncated and non- functional death domain and has been reported to promote activation of NF-κB, However as the decoy receptors are capable of binding TRAIL they reduce DR4 and DR5 apoptotic signaling by competing for ligand binding.[64]

DR6

DR6 is highly conserved and was originally identified for novel members of the TNF-R superfamily. Comparative sequence analyses indicated that DR6 contains a death domain, which is unusually located adjacent to the transmembrane domain, but not at the C-terminal end of the molecule as in other death receptors. Preliminary over-expression studies showed that DR6 interacts weakly with type 1-associated death domain, but not with Fas-associated protein with death domain, via its death domain. While DR6 robustly activates the JNK pathway independently of its death domain, only a moderate capacity of the receptor to induce NF-κB or apoptosis upon over-expression has been reported. [65] Mice with targeted disruption of the DR6 show increased cell expansion, and enhanced survival and humoral responses of activated B-cells [66,67] They also display enhanced $CD4^+$ T-cell proliferation and increased Th2 cytokine production. This phenotype correlates with an increase in nuclear cRel, a member of the NF-κB family, and nuclear factor of activated T-cells c (NF-ATc) in B- and T-cells, of DR6-deficient mice [68] there is also reduced JNK activity in activated $CD4^+$ T-cells of DR6 mice. The increase of nuclear NF-ATc in these cells, because JNK has an inhibitory effect on calcineurin-mediated activation of NF-ATc. Although enhanced B-cell proliferation in DR6 deficient mice is partly associated with reduced apoptosis, this effect reflects increased activity of cRel, rather than direct DR6 mediated triggering of apoptosis. Thus together, these data suggest that DR6 fulfills its immune-regulatory functions largely independently from direct apoptosis induction. Very little is known about the mechanisms that control death signaling from DR6. [69]

EDAR

The EDAR gene was identified in association with the condition ectodermal dysplasia, which is also caused by a mutation in the EDAR- associated death domain protein [70, 71]. The EDAR gene, which contains a polymorphism common in Han Chinese populations, is required for the development of the ectoderm that gives rise to skin, hair, nails, teeth, and mammary and sweat glands, and has been most widely studied in this developmental context [72]. EDAR does not interact with type 1-associated death domain or fas-associated protein with death domain but, via EDGAR- associated death domain protein, signals through the TRAF family members 3 and 6 to activate JNK and NF-κB, thereby regulating the gene transcription required for the development of ectoderm appendages. [73, 74]

P^{75NTR}

P^{75NTR} is a receptor for the neurotrophin family of growth factors and mediates a wide range of cellular outcomes, predominantly in the nervous system. The best-known function of P^{75NTR} is to promote apoptosis in the developing nervous system as neurons undergo selection during the period of synaptogenesis [75]. It also

causes neurodegeneration after injury or in neurological conditions, including motor neuron disease and Alzheimer's disease [76]. P^{75NTR} mediates cell death by the mitochondrial death pathway, as it is inhibited in cells from Apaf1-and Bax-deficient animals and is blocked by BclxL and intracellular potassium (which inhibit cytochrome activation of the apoptosome [77,78] Like Fas, P^{75NTR} can generate ceramide, and its cell death signaling requires lipid-rich regions of the membrane and the palmitoylation of the receptor [79,80]. However, like EDAR, P^{75NTR} does not interact with Fas-associated protein with death domain or type 1-associated death domain; although a dominant-negative type 1-associated death domain mutant was found to inhibit P^{75NTR} mediated NF-κB activation [81, 82]. Unlike the death domains in other DRs, the P^{75NTR} death domain does not self-associate and cannot substitute for the Fas death domain, having a different tertiary structure to that of the other family members [83, 84] Nonetheless, P^{75NTR} signals via protein-protein interactions, including binding to RIP2 and TRAF2, 4, and 6 ·In addition, it interacts with NRIF and NRAGE, adaptor proteins that activate JNK to promote cell death. Alternatively, P^{75NTR} can bind to RIP2 to activate NF- κB, and it can also activate RhoA, to produce act in remodeling.[85]

THE PHYSIOLOGICAL ROLE OF DEATH RECEPTORS

Most death receptors generate multiple signals leading to a variety of biological responses. This pleiotropic aspect of death receptor signaling is best documented for TNF-a. TNFR-1-1- mice have deficient defenses against certain intracellular pathogens and a compromised immune response. [86, 87] Other recent reviews can be consulted for a complete description of all the effects of TNF-α**.** [88, 89] The naturally occurring *lpr* and *gld* mice have defects in Fas and FasL, respectively. [90] These mice suffer from lymph proliferative disease manifesting itself in the expansion of lymphoid organs implicating Fas and FasL in lymphoid survival. To date gene targeting experiments have not been reported on TRAIL and their receptors. Therefore, the physiological role of this ligand-receptor system remains poorly defined; however, such information would be of great interest for estimating the potential side effects in settings in which TRAIL is used as a cancer therapeutic agent. [91] Many detailed analyses have been performed on the P^{75NTR}mice. [92] The main deficit is in the peripheral nervous system. [93] Sympathetic, trigeminal, and cholinergic forebrain neurons are also affected. In accordance with a pro-apoptotic role for P^{+} increase number of neurons or neurons that die more slowly are found in P^{75NTR} mice; however, activation of P^{75NTR} can also lead to increased cell migration and enhance the pro-survival effects of TrkA. [94, 95]

DEATH RECEPTORS AS PHARMACOLOGICAL TARGETS

The potential to use activation of death receptors to combat malignancies predates the characterization of these proteins at a molecular level. [96] Experiments with injection of recombinant TNF-a into mice carrying a tumor burden revealed that the tumoricidal activity was caused by destruction of the vasculature of the tumors rather than because of the destruction of the tumor itself. [97] Consequently the effective doses are also often lethal. This severe toxicity is also a problem for approaches that aim at inhibiting the NF-KB pathway to down-regulate the inflammatory response. Severe TNFR-1-mediated liver toxicity results if NF-KB is inhibited throughout development.[98] Similarly, injection of recombinant FasL or agonistic Fas antibody causes death within hours owing to liver toxicity.[99] A more promising approach is the administration of recombinant TRAIL. Doses that are effective for tumor regression are tolerated well by mice. [100]

DEATH RECEPTOR SIGNAL TRANSDUCTION MECHANISM PROCESSES

The Initiation of signal transduction requires the oligomerization of the receptor and the intracellular domains [101]. Receptor trimerization was initially thought to be triggered by the binding of the ligand in the receptors extracellular domain. This concept has been challenged by the existence of receptor oligomers on the cell surface [102] the formation of these ligand-independent receptor complexes occurs through the interaction of domain a region termed the pre-ligand assembly domain (PLAD). While PLAD is not directly involved in

ligand binding,[103] Ligand-independent receptor complex formation has also been suggested for TRAIL and Fas receptors [104, 105]. Ligand binding causes a conformational change in the receptor, which leads to recruitment of different adaptor proteins *i.e*., Fas-associated protein with death domain (Fas-associated protein with death domain) and TNF receptor-associated protein with death domain, (type 1-associated death domain) These proteins couple death receptor ligation to the activation of cell death effectors, namely, the initiator caspases (caspase 8 and caspase 10). Adaptor molecules are able to associate with the receptors through homotypic interaction of their death domain with the receptor's death domain. They may also contain additional protein-protein interaction modules, such as death effector domains that mediate the recruitment of caspases. The resulting complex is termed the death-inducing signaling complex and can generate an apoptotic signaling cascade initiated by the activated caspases. [106] The mechanism of activation the enzyme is released into the cytosol in an active heterotetrameric form containing two large and two small subunits, which, in turn, triggers a proteolytic cascade. Activation of caspase 8 and 10 at the DISC can be regulated by cFLIP [107]. Several c-FLIP variants are generated by alternative mRNA splicing, but only three of them are expressed at the protein level, the most abundant cFLIP long (cFLIPL), a cFLIP short (cFLIPS)[108]. The role of cFLIPS in inhibiting death receptor-mediated apoptosis is well established. CFLIPS was shown to block caspase-8 processing and activation at the DISC, probably by competing for binding and recruitment to Fas-associated protein with death domain. It is likely that the two proteins inhibit death receptor-mediated apoptosis through similar mechanisms. On the contrary, the function of cFLIPL at the DISC remains controversial [109]. Originally, similarly to cFLIPS, cFLIPL was described as an antiapoptotic molecule that inhibits death receptor-induced apoptosis by interfering with caspase 8 activation at the DISC [110,111]. Indeed, over expression of cFLIPL results in recruitment of both cFLIPL and caspase 8 to the DISC, followed by defective processing of caspase 8, with the cleaved intermediates remaining bound to the DISC, and no generation of the active heterodimeric form[] In addition, several reports have implicated cFLIPL in the activation of survival signaling [112] pathways, such as NF-KB- and MAPK-regulated pathways, after death receptor-treatment, due to its ability to recruit adaptor proteins involved in these signaling pathways [113, 114]. These results suggest that FLIPL has a dual function, as either inhibitor or promoter of caspase activation, with its role being determined by a variety of factors, including its expression level and cellular levels relative to caspase 8 [115]. The amount of active caspase 8, and perhaps caspase 10, released into the cytosol likely determines the apoptosis signaling pathways initiated downstream of the DISC. Large amounts of active caspase 8 start a cascade of caspase activation by directly processing and activating the so-called effector caspases, which then proceed to cleave and degrade several crucial cellular proteins. Alternatively, small amounts of caspase 8 depend on cleavage of the proapoptotic BH3-only protein Bid to induce cell death. This truncated carboxy-terminal fragment (tBid) translocates to the mitochondria, causing oligomerization of the proapoptotic, multidomain Bcl-2 proteins Bax or Bak, which, in turn, mediate the mitochondrial pathway of cell death [116-119]. In recent years, it has become evident that the nature of the signal transduction events originating from the death receptors is determined by the formation of spatially and temporally distinct receptor/adaptor complexes. Within these complexes, the receptor-interacting protein 1 (RIP1), a DD-containing serine/threonine kinase, plays a crucial role in switching between death and survival signaling. RIP1 binds to all death receptors, as well as to DD-containing adaptors like FAS-ASSOCIATED PROTEIN WITH DEATH DOMAIN and TYPE 1-ASSOCIATED DEATH DOMAIN, *via* interaction with its own death domain [120]. Deubiquitination of RIP1 results in the enhanced formation of RIP1/FAS-ASSOCIATED PROTEIN WITH DEATH DOMAIN /caspase 8 complexes, and consequent caspase 8 activation and apoptosis [121]. During death receptor-mediated apoptosis, RIP1 is cleaved and inactivated by caspase 8, providing a mechanism to silence RIP1-activated survival signaling [122]. Finally, RIP1 may also act as a central initiator of Fas-mediated necrosis in cells lacking caspase 8 [123]. Although the above molecules and pathways are common to all death receptors, their assembly and execution is unique to each death receptor and will now be reviewed in detail.

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