Multiple Molecular Targets of Sensitizers in Tumor Necrosis Factor (TNF)-Related Apoptosis–Inducing Ligand (TRAIL/Apo2L)–Mediated Apoptosis

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Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL/Apo2L) is a recently identified member of the TNF ligand family that can initiate apoptosis through the activation of their death receptors. TRAIL has been paid attention as a potential anti-cancer drug, because it selectively induces apoptosis in tumor cells in vitro and in vivo but not in most normal cells. However, recent studies have shown that some cancer cells including malignant renal cell carcinoma and hepatocellular carcinoma, are resistant to the apoptotic effects of TRAIL. Therefore, single treatment with TRAIL may not be sufficient for the treatment of various malignant tumor cells. Understanding the molecular mechanisms of TRAIL resistance and identification of sensitizers capable of overcoming TRAIL resistance in cancer cells is needed for the establishment of more effective TRAIL-based cancer therapies. Chemotherapeutic drugs induce apoptosis and the upregulation of death receptors or activation of intracellular signaling pathways of TRAIL. Numerous chemotherapeutic drugs have been shown to sensitize tumor cells to TRAIL-mediated apoptosis. In this study, we summarize biological agents and drugs that sensitize tumors to TRAIL-mediated apoptosis and discuss the potential molecular basis for their sensitization.

Key words: TRAIL, death receptor, sensitization, cancer therapy

Introduction

Apoptosis is an important regulatory mechanism on development, tissue homeostasis, immune response, and elimination of damaged cells and non-necessary cells. Apoptosis is tightly controlled and demand energy. Balance between cell death and cell survival maintain healthy tissue, organ, and body. Unfortunately, deregulation of apoptosis leads to cancer, and then contributes to malignant tumor.

In mammals, apoptosis was induced via distinct two pathways. One is an intrinsic pathway that is activated by intracellular signals, such as DNA damage, excessive reactive oxygen species, and hypoxia. Intracellular signals, which stimulate intrinsic pathway, result in opening of the mitochondrial transition pore. Successively, mitochondrial transmembrane potential is lost, and pro-apoptotic proteins, such as cytochrome c, apoptosis-inducing factors, Omi/HtrA2, EndoG and Smac/DIABLO, released from intermembrane space to cytoplasm. Released cytochrome c forms apoptosome, which is composed of apoptotic protease-activating factor (Apaf), cytochrome c and caspase-9.

Caspase-9 induces activation of caspase-3, 6, and 7. Omi/HtrA2 and Smac/DIABLO bind to inhibitors of apoptosis, thus induce to disrupting complex of inhibitors of apoptosis protein (IAP) and caspase-3 or 9. The other is an extrinsic pathway. Activation of death receptor is involved in this pathway. Tumor necrosis factor (TNF) family of cytokines, such as TNF, Fas ligand, and TNF-related apoptosis-inducing ligand (TRAIL), bind to their receptor, and recruit caspase-8 into a death inducing signalling complex (DISC) at the plasma membrane. Caspase-8 activation leads to cleave caspase-3 (active form) or induce outer mitochondrial membrane permeabilization, and then release cytochrome c Among of them, TRAIL-mediated apoptosis is promising tumor therapeutic. TRAIL selectively induces apoptosis in tumor cells, but does not cause toxicity to most normal cells, which is supported by the presence of large numbers of decoy receptors on normal cells [29].

However, although TRAIL is a charming agent to treatment against tumor cells, many papers reported that a lot of tumor cells have resistance or change into TRAIL-induced apoptosis resistant cells. TRAIL-resistant cancer cells can be sensitized by chemotherapeutic drugs in vitro and in vivo indicating that combination therapy could induce sensitivity of tumor cells against TRAIL. Therefore, understanding the
molecular mechanisms of TRAIL resistance and ways to sensitize tumor cells to undergo apoptosis by TRAIL are important points for effective cancer therapy.

Multiple molecular targets of sensitizers in the TRAIL-mediated apoptosis

TRAIL

Wiley et al. and Petti et al. first discovered TRAIL [31,49]. TRAIL is composed of five exons of 222, 138, 42, 106, and 1245 nucleotides and four introns of 8.2, 3.2, 2.3, and 2.3 kb, and located on chromosome 3. While TRAIL genes lack TATA and CAAT boxes, the promoter of TRAIL include putative response elements for GATA, activator protein a (API), CCAAT/enhancer binding protein (C/EBP), specific protein-1 (SP-1), octamer-binding transcription factor 1 (OCT-1), AP3, polymavirus enhancer activator 3 homolog (PEA3), cleavage stimulation factor (CF-1), NF-κB, and interferon-sensitive response element (ISRE) [17,46].

Most tissue is detected TRAIL expression in human. For examples, TRAIL was detected by immunohistochemistry in hepatocytes and bile duct epithelium of liver, neurons of brain, tubuli contorti of kidney, myocytes of heart, luminal epithelium and crypt cells of colon, bronchial epithelium, alveolar septa, and vascular endothelium of lung, germ cells and Leydig cells of testis, and immune cells, such as natural killer cells, macrophages, T cells and dendritic cells [35]. Furthermore, spleen and prostate also expressed TRAIL [49].

TRAIL, which is a member of TNF superfamilies, anchored to the cell membrane, carboxyl terminus is located in extracellular space, and has the receptor binding domain as a type II transmembrane polypeptide of 281 amino acids. Cleavage of C-terminal domain of TRAIL by cysteine protease makes soluble TRAIL. TRAIL is composed of two anti-parallel β-pleated sheets, which form a β sandwich, and then binds to the adjacent TRAIL monomer to form a homotrimer. TRAIL acts as a homotrimer and this homotrimer has stronger biological activity than monomer of TRAIL. Cysteine residue at position 230 of TRAIL is important for stability and activity as zinc ion bind to cysteine residue [2].

TRAIL receptors

TRAIL could bind to five different membrane receptors; Death receptor 4 (DR4; TRAIL-R1), DR5 (TRAIL-R2), decoy receptor (DcR1; TRAIL-R3), DcR2 (TRAIL-R4), and Osteoprotegerin (OPG) [8]. There is a different functionally between death receptors and decoy receptors. Death receptors have a cytoplasmic death domain, which could recruit apoptosis signalling molecules, and trigger apoptosis. On the other hands, decoy receptors lack cytoplasmic death domain, and inhibit apoptosis by death receptor as sequester TRAIL in extracellular space. OPG, as soluble protein, could bind to TRAIL with low affinity.

Apoptosis signalling by TRAIL receptor

TRAIL homotrimer binds to death receptors, DR4 and DR5, and then recruit FAS-associated protein with death domain (FADD) via interaction of death domain in the carboxyl terminus of receptor. FADD, as an adaptor protein, recruits caspase 8 or 10 via death effector domain (DED), and then forms the death inducing stimulation complex (DISC). DISC could trigger activation of initiating caspase via inducing autocatalytic processing, and caspase is released into cytoplasm. Activated initiating caspase induces activation of effector caspase-3, 6, and 7. In type I cells, activation of caspase-8 via formation of DISC is sufficient to induce apoptosis. However, in type II cells, mitochondria pathway is involved in induction of apoptosis. Caspase-8 or 10 cleaves Bid into truncated Bid (tBid), which in turn translocates to the mitochondria and then induces the activation of Bcl-2-antagonist/killer (Bak) and Bcl2-associated X protein (Bax), pro-apoptotic protein. Activated Bak and Bax change the mitochondrial membrane potential, and release cytochrome c into cytoplasm.

Non-apoptosis signalling by TRAIL receptor

TRAIL could also activate non-apoptotic signalling depending on the cell types, duration and strength of signal, and recruiting down stream signalling molecules. TRAIL induces activation of nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPKs), protein kinase B/Akt via various combination of signalling proteins, such as FADD, TNFR type I- associated death domain protein (TRADD), caspase-8, 10, cellular FLICE-like inhibitory protein (c-FLIP), TNF receptor associated factor 2 (TRAF2), and RIPA-interacting protein (RIP) [5,33,40].

Physiological signaling by TRAIL receptor

TRAIL signalling is associated with immune system. Monoocytes, T cells, dendritic cells, and natural killer cells increased TRAIL (soluble and membrane bound form) ex-
pression by several stimuli, such as interferon, and expression of TRAIL in monocytes and dendritic cells is correlated with cytotoxicity against tumor cells [1]. Therefore, TRAIL signalling is involved in immune response. In addition, TRAIL is regarded as tumorigenesis and metastasis. In TRAIL knock out mice or mice treated with antibody blockade of TRAIL, tumor growth and metastasis are promoted [4,36]. In contrast, a few papers were reported that TRAIL is not associated with tumorigenesis in intestinal and skin tumor [9,51].

**TRAIL as therapeutic agent**

TRAIL is a potent anti-cancer agent, promotes apoptosis in tumor cells, while has no or minimal effects on death of normal cells, because level of decoy receptors is higher in normal cells than in tumor cells. Soluble TRAIL and monoclonal antibodies, anti-DR4 and anti-DR5, are selectively induced apoptosis in tumor cells. TRAIL is a promising therapeutic agent for the treatment of cancer. However, therapy using TRAIL is limited to TRAIL-sensitive tumor. In recently, many researchers were reported that a number of cancer cells are resistant to TRAIL, such as pancreatic cancer, neuroblastoma, chronic lymphocytic leukaemia (CLL), astrocytoma, meningioma, medulloblastoma and malignant melanoma. Therefore, we need more efficient therapeutic strategy.

**Mechanism of resistance to TRAIL**

Apoptosis by TRAIL is modulated at several stages in the apoptotic signalling pathways. Tumor cells could escape from apoptosis via activation of survival mechanisms. Therefore, we need to study for TRAIL-resistant mechanisms.

**Death receptor expression**

TRAIL resistant is associated with 8p chromosome deletion. Death receptors are located on this sites, which is a hot-spot for deletions and frequently appear allelic loss [18]. Down-regulation of death receptor was detected in several cancer types, such as non-Hodgkin's lymphoma and non-small cell lung cancers, head and neck cancers, gastric cancers, and breast cancers [7]. Hypermethylation of TRAIL gene decreases TRAIL receptor gene expression, and down-regulation of death receptor is one of TRAIL-resistant mechanism [43]. Furthermore, post-translational mod-

ification of the death receptor changes signal transition by TRAIL. O-glycosylation of death receptor promotes TRAIL-induced clustering of DR4 and DR5. O-glycosylation by GALNT14, a O-glycosyltransferase, increases response against TRAIL in pancreatic carcinoma, non-small-cell lung carcinoma and melanoma cell lines [44]. S-palmitoylation of DR4 is also involved in oligomerization of DR4, and then promotes TRAIL-induced signalling [44].

**c-FLIP and caspase-8 expression**

TRAIL-resistance is correlated with c-FLIP expression in lung and breast cancers, colon and hepatocellular carcinoma, malignant melanoma, leukemia, and glioblastoma. c-FLIP competes with caspase-8 for DISC binding sites, thus high levels of c-FLIP could block cleavage of caspase-8. Thus, c-FLIP inhibits TRAIL-induced death signal. Furthermore, some cells, such as lung carcinoma, neuroblastoma, leukemia, and colon cells, are expressed low levels of caspase-8. Methylation and point mutation of genes results in low levels of caspase-8 expression [39].

**Modulation of components in mitochondria**

Bcl-2 family is divided into two groups, pro-apoptotic
(Bax and Bak) and anti-apoptotic (Bcl-2 and Bcl-xl). Overexpression of Bcl-2 or Bcl-xl blocked TRAIL-induced apoptosis in adenocarcinoma and pancreatic carcinoma, and inactivation of Bax and Bak also failed to induce apoptosis by TRAIL in some cells, such as solid tumor and colon carcinomas and colorectal cancer cells [44,42,52]. Balance of Bcl-2 family between pro-apoptotic protein and anti-apoptotic protein decides sensitivity against TRAIL. Therefore, although TRAIL induces extrinsic apoptosis, crosstalk between death receptor signalling and mitochondrial signalling is associated with TRAIL-induced apoptosis.

IAP family contains baculovirus IAP repeat (BIR domain), which could bind caspases, and C-terminal RING domain, which ubiquitinate. When IAP make complex with caspase, they ubiquitinate and then degrade. Member of IAP contain X-linked IAP (XIAP), c-IAP1, c-IAP2, survivin, livin, tS-IAP, ILP-2 and Bruce. Among of them, XIAP has the most potent function and bind caspase 3, 7, and 9. Overexpression of IAPs is associated with TRAIL resistance [28].

Modulation of signalling pathways

PI3K/Akt signalling is involved in expression of c-FLIP, XIAP, and Bcl-2 [48, 30]. Increased expression of these proteins induces inactivation of Bax, Bad, and caspase. Therefore, activation of PI3K/Akt increases resistance against TRAIL. In fact, increased activation of PI3K/Akt signalling is already reported in TRAIL-resistant cells, such as colon cancer, gastric cancers, and leukemia [23,32,47].

MAPKs is identified three subfamilies; ERK, JNK, and p38 MAPK. The role of MAPK is controversial on TRAIL-induced apoptosis. ERK has been known as survival signalling. In breast cancer cells, activation of ERK inhibits TRAIL-induced apoptosis [20], while inhibition of JNK signalling induces TRAIL-sensitize in hepatocellular carcinoma cells [27]. In contrast, activation of JNK and p38 MAPK enhance TRAIL-induced apoptosis in hepatocellular carcinoma [45]. Therefore, understanding about role of MAPKs on TRAIL-induced apoptosis needs more information and further studies.

The role of NF-kB signalling on TRAIL-induced apoptosis is also controversial. TRAIL homotrimer binds DR4 or DR5, and could activate NF-kB signalling [13]. XIAP could enhance of 1κB degradation, and then increase NF-kB activity [10, 22]. Thus, activation of NF-kB desensitizes cells to TRAIL. However, in the TRAIL-resistant cells, NF-kB has an apposite function, that is, NF-kB induced proliferation and survival [6]. There is one of possibility to determine death or life. The component of NF-kB has a different function. Rel A (p65) acts as anti-apoptotic signalling. Overexpression of RelA induced c-IAP and decreased DR expression. On the other hands, c-Rel acts as a pro-apoptotic signalling, which increase DR expression and decrease IAPs expression [3].

Strategies to induce TRAIL sensitivity

As mentioned earlier, tumor cells have exhibit resistance to TRAIL-induced apoptosis. Therefore, to induce cellular apoptosis need a new therapeutic strategy. Previous studies reported that TRAIL induced tumor cells apoptosis in the presence of other chemopreventive drugs, such as curcumin, withaferin A, luteolin, quercetin, resveratrol, and silybin, which restore TRAIL sensitivity. The sensitizing mechanisms of these drugs are diverse; 1) up-regulation of death receptor (DR) expression levels [14], 2) decrease of c-FLIP expression [21], 3) up-regulation of pro-apoptotic components and down-regulation of anti-apoptotic components in Bcl-2 family [41], 4) reduction of IAPs family [19], 5) modulation of signalling molecules.
Novel strategy via modulation of TRAIL-related components

Up-regulation of death receptor: Curcumin and Calyculin A

Curcumin is a very famous flavoring agent in foods, and is a major component of the Curcuma species. Previous studies reported that curcumin have a antiproliferative activity and anticancerogenic activity in vitro and in vivo [11,24]. However, the mechanisms underlying the effects of curcumin on cancer cells are not understood. Curcumin enhanced TRAIL-induced cell death in Caki cells, renal cancer cell line (Fig. 3A). Furthermore, Treatment with curcumin and TRAIL in Caki cells increased typical ladder pattern of internucleosomal fragmentation, which is a hallmark of apoptosis (Fig. 3B). Molecular mechanisms underlying the synergistic induction of apoptosis by curcumin and TRAIL in Caki cells is an up-regulation of DR5 (Fig. 3C). Treatment with curcumin induced the expression of DR5 protein in a dose-dependent manner. These results suggest that curcumin enhances TRAIL-induced apoptosis by DR5 upregulation in Caki cells.

State of phosphorylation and dephosphorylation is important on transition cellular signal. Phosphorylation is modulate by protein kinases, such as MAPK, protein kinase A, protein kinase C, and PI3K/Akt. On the other hands, protein phosphatases (PPs) restore protein to dephosphorylated state. The balance between kinase and phosphatase is key regulator for the cellular signalling cascade. Phosphatase is divided into four groups as their substrates; 1) serine/threonine phosphatase, 2) protein histidine phosphatase, 3) protein tyrosine phosphatase, and 4) dual-specific phosphatase. Among them, we have an interesting on serine/threonine phosphatase. Calyculin A has known as a potent serine/threonine phosphatase inhibitor, and it inhibits phosphatase 1 and 2.

In previous studies, inhibitors of phosphatase induced tumor cell apoptosis. Interestingly, calyculin A increased apoptosis in human osteoblastic osteosarcoma MG63 cells [37]. As shown in Fig.4A and B, calyculin A significantly induced DR4 protein and mRNA expression in a dose-dependent manner. This data indicate that calyculin A may regulate expression of TRAIL sensitizing components. Caki cells are not induced apoptosis by TRAIL alone. However, when Caki cells were co-treated with calyculin A and TRAIL, sub-G1 phase cells increased (Fig. 4C). In addition, DR4 expression was dramatically increased in calyculin A and TRAIL co-treated Caki cells, compared with calyculin A alone (Fig. 4D). This result suggest that calyculin A-mediated TRAIL sensitization is an attractive strategy for treatment of TRAIL-resistant cancer cells.

![Fig. 3. The effect of curcumin on TRAIL-sensitization in Caki cells (A-C) Caki cells were treated with TRAIL (100 ng/ml) in the absence or presence of curcumin (30 μM). (A) Apoptosis was analyzed as a sub-G1 fraction by FACS. (B) Fragmentation of genomic DNA in Caki cells treated with 100 ng/ml TRAIL and 30 μM curcumin for 24 hr. (C) Caki cells were treated with indicated concentrations of curcumin. DR5 protein expression was determined using Western blotting.](image-url)
Fig. 5. The effect of Withaferin A (Wit A) on TRAIL-sensitization in Caki cells. (A) Caki cells were treated with indicated concentrations of Wit A for 24 hr. c-FLIP protein expression was determined using Western blotting. (B and C) Caki vector and Caki/c-FLIP cells were treated with 100 ng/ml TRAIL in the absence or presence of 1.2 μM Wit A for 24 hr. Apoptosis was analyzed as a sub-G1 fraction by FACS (B). Cleavage of PARP was also significantly inhibited by overexpression of c-FLIP (Fig. 5C). These results indicate that down-regulation of c-FLIP is associated with withaferin

Down-regulation of cFLIP: Withaferin A

Withaferin A is a steroidal lactone isolated from the medicinal plant *Withania somnifera*. It has been known as an important prototype of the withanolide class of natural products. Previous studies reported that withaferin A inhibited tumor cell growth, metastasis and angiogenesis [26, 50]. In addition, withaferin A significantly inhibited c-FLIP expression in a dose-dependent manner in Caki cells (Fig. 5A). Furthermore, overexpression of c-FLIP in Caki cells (Caki/c-FLIP) inhibited withaferin A–facilitated TRAIL-induced apoptosis, compared with that of Caki/vector cells (Fig. 5B). Cleavage of PARP was also significantly inhibited by overexpression of c-FLIP (Fig. 5C). These results indicate that down-regulation of c-FLIP is associated with withaferin.
A-enhanced TRAIL-induced apoptosis.

Down-regulation of XIAP; Mithramycin A

Mithramycin A (also known as Plicamycin), which is an anticancer and antibiotic agent, was isolated from streptomycetes griseus. Mithramycin A have an anticancer effects via interaction with double-stranded DNA with GC base specificity in genes promoter [25]. Furthermore, mithramycin A could regulate expression of TRAIL sensitized components. Caki cells treated with mithramycin A was significantly inhibited XIAP expression (Fig. 6A). Overexpression of XIAP (Caki/XIAP) was inhibited apoptosis and PARP protein expression were determined using Western blotting (C).

Fig. 6. The effect of Mithramycin A (Mi A) on TRAIL-sensitization in Caki cells (A) Caki cells were treated with the indicated concentrations of Mi A in the absence or presence of 100 ng/ml TRAIL for 24 hr. (B and C) Caki/vector and Caki/XIAP cells were treated with 200 nM Mi A and 100 ng/ml TRAIL for 24 hr. Apoptosis was analyzed as a sub-G1 by FACS (B). XIAP and PARP protein expression were determined using Western blotting (C).

Fig. 7. The effect of Kahweol (Kah) on TRAIL-sensitization in Caki cells (A and B) Caki cells were treated with the indicated concentrations of Kah in the absence or presence of 100 ng/ml TRAIL for 24 hr. Apoptosis was analyzed as a sub-G1 fraction by FACS (A). Bcl2 protein expression was determined using Western blotting (B). (C and D) Caki/vector and Caki/Bcl2 cells were treated with 20 μM and 50 ng/ml TRAIL for 24 hr. Apoptosis was analyzed as a sub-G1 by FACS (B). Bcl2 and PARP protein expression were determined using Western blotting (D).
expression in mithramycin A and TRAIL-treatd cells, compare with Caki/vector cells (Fig. 6B and C).

Down-regulation of Bcl-2: Kahweol

Kahweol is a diterpene molecule, that is found in coffee beans. The compound have a multiple functions, such as anti-cancer, anti-tumor, and anti-inflammation [12,16,38]. Kahweol acts as anti-carcinogenic drugs through induction of phase II detoxifying enzymes and reduction of signal transducer and activator of transcription 3 (STAT 3) [15,38]. In addition, kahweol sensitized TRAIL-induced apoptosis in Caki cells. As shown in Fig. 7A, kahweol induced TRAIL-mediated cell death in a dose-dependent manner. Bcl-2 expression also blocked in kahweol and TRAIL-treated cells, compare with kahweol or TRAIL alone (Fig. 7B). Overexpression of Bcl-2 (Caki/Bcl-2) significantly decreased TRAIL-induced cell death in the presence of kahweol, compare with Caki/vector (Fig. 7C). Cleavage of PARP also blocked in Caki/Bcl2 cells (Fig. 7D). Therefore, kahweol enhanced TRAIL-sensitization via down-regulation of Bcl2.

Conclusion

TRAIL has been known as a potent anti-cancer drug, because TRAIL specifically induces apoptosis in tumor cells, not normal cells. However, some cancer cells have a resistance against TRAIL, through induction of c-FLIP, IAPs, and anti-apoptotic Bcl2 family expression, and reduction of DR4, DR5, and pro-apoptotic Bcl2 family expression. Single treatment with TRAIL is not sufficient strategy to induce apoptosis in tumor cells. Several agents, such as curcumin, calyculin A, withaferin A, mithramycin A, and kahweol, could enhance sensitivity against TRAIL through modulation of TRAIL-related signal components (Fig. 8). Therefore, we need to understand the mechanism of TRAIL-resistance and find a novel TRAIL-sensitizing drug for cancer therapy.

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References


초록: TRAIL 매개의 세포사멸 유도를 위한 다양한 분자적 타깃

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TNF ligand 군에 속하는 Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL/Apo2L)은 death receptor를 통한 세포사멸을 유도하는 것으로 알려졌다. TRAIL은 정상세포에서는 세포사를 일으키지 않고 암세포에서는 특이적으로 세포사멸을 유도함으로써 임상적으로 유용한 항암제로 주목받고 있다. 그러나, 최근 연구에 의하면 악성 신장암과 간암과 같은 일부 암에서는 TRAIL에 의한 세포사멸 저항성을 가진 것으로 알려져 있다. 그러므로, TRAIL 만으로는 다양한 악성종양을 위한 치료법으로 적절하지 않다. TRAIL에 대한 저항성을 가지는 분자적 기전을 이해하고, TRAIL 저항성을 극복할 수 있는 증강제를 밝혀내는 것이 보다 효율적인 TRAIL을 이용한 암세포 치료 전략에 필요하다. 화학치료제들이 TRAIL 수용체인 death receptor의 발현을 증가시키고, 세포 내의 TRAIL에 의한 신호전달 체계를 활성화 시키는 것으로 알려져 있고, 이러한 기전을 통하여 다양한 화학치료제들이 TRAIL에 의한 세포사멸 증가시키는 것을 확인하였다. 이 논문에서, 우리는 TRAIL에 의한 세포사멸을 증가시키기 위한 생물학적 약물들을 정리하고, 그 분자적 기전을 고찰한다.