PRACA POGLĄDOWA

Tumor Necrosis Factor-related apoptosis inducing ligand (TRAIL) and its receptors

Ligand czynnika martwicy nowotworu (TRAIL) i jego receptory

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ABSTRACT

Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) is a cytokine of the tumor necrosis factor (TNF) superfamily. The mRNA for TRAIL is expressed in most of the normal human cells and tissues, including T cells, monocytes, macrophages, dentritic cells, natural killer cells (NK) and spleen, lung, prostate. The most important biological function of this cytokine is inducing apoptosis in cancer, transformed cells with little or no cytotoxity against non-transformed cells and tissues and thus TRAIL is promising anticancer cytokine. TRAIL induces programmed cell death through interacting with its receptors. Five TRAIL receptors have been identified: TRAIL-R1 and TRAIL-R2 have ability to initiate the apoptosis-signaling cascade after ligation, whereas "decoy receptors"-TRAIL-R3, -R4 and osteoprotegerin (OPG) lack this ability. TRAIL induces apoptosis in several tumor cell lines, but many primary tumors are resistant to TRAIL-induced apoptosis. Several mechanisms underlying TRAIL resistance have been proposed. Thus, scientists are currently attempting to identity TRAIL sensitizers that are able to overcome TRAIL resistance in cancer cells. The chemotherapy agents, radiation, lipopolysaccharide, interferons, flavonoids are capable of enhancing TRAIL-induced apoptosis in cancer cells.

KEY WORDS
TRAIL, TRAIL-receptors, apoptosis, cancers, TRAIL-resistance

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STRESZCZENIE

Ligand czynnika martwicy nowotworu (TRAIL) jest cytokiną należącą do nadrodziny czynnika martwicy nowotworów (TNF). Ekspresję mRNA dla TRAIL stwierdzono w wielu prawidłowych komórkach i tkankach organizmu: limfocytach T, monocytach, makrofagach, komórkach dendrytycznych, komórkach *natural killer* (NK), a także w śledzionie, płucach, gruczole krokowym. Najważniejszą funkcją biologiczną tej cytokiny jest indukowanie apoptozy w komórkach nowotworowych, transformowanych,

bez działania cytotoksycznego w stosunku do niezmienionych komórek i tkanek, dlatego TRAIL jest obiecującą cytokiną antynowotworową. TRAIL indukuje programowaną śmierć komórki poprzez interakcje ze swoimi receptorami. Zidentyfikowano pięć receptorów TRAIL: TRAIL-R1 i TRAIL-R2, mających zdolność inicjowania sygnału do apoptozy po połączeniu z ligandem, oraz „receptory pułapki" – TRAIL-R3 i TRAIL-R4, osteoprotegeryna (OPG) – nieposiadające tej zdolności. TRAIL indukuje apoptozę wielu linii komórek nowotworowych, jednak wiele pierwotnych nowotworów jest opornych na apoptozę indukowaną TRAIL. Zaproponowano wiele mechanizmów leżących u podstaw tej oporności. Naukowcy starają się zidentyfikować czynniki uwrażliwiające komórki nowotworowe w celu przełamania ich oporności na TRAIL. Chemioterapia, promieniowanie, lipopolisacharyd, interferony, flawonoidy są zdolne usprawniania apoptozy indukowanej TRAIL w komórkach nowotworowych.

SŁOWA KLUCZOWE
TRAIL, receptory TRAIL, apoptoza, nowotwory, oporność na TRAIL

TUMOR NECROSIS FACTOR-RELATED APOPTOSIS INDUCING LIGAND (TRAIL)

Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) is a novel member of the Tumor Necrosis Factor (TNF) superfamily. TRAIL is present as a type II transmembrane protein-N-terminal located in the cell interior and C-terminal on the exterior. TRAIL protein consists of 281 amino acids in its human form. The percent identity of the extracellular C-terminal domain of this cytokine to the most closely related members of the TNF ligand family such as Fas ligand, TNFα, LTα, LTβ is 28%, 23%, 23% and 22% respectively. Although has short intracellular domain (17 amino acids) [1,2,]. This protein is synthesized in a pro-form with a signal sequence that is removed in the mature secreted protein. TRAIL can also be anchored in the membrane via hydrophobic amino acids (memTRAIL) or release as soluble protein (sTRAIL). TRAIL can form monomer or homotrimer. This trimerization enhances biological activity of this cytokine as compared to monomeric form. Monomers TRAIL are made up of two antiparallel β-pleated sheets interact in a head-to-tail fashion to form a bell-shaped trimer. Additionally, TRAIL monomer of native sequence contains a single cysteine at position 230 (Cys 230) and zinc atom for trimer stability, integrity and optimal biological activity. The gene encoding TRAIL is located on human chromosome 3q26 [3,4,5,6,7].

The mRNA for TRAIL is expressed in most of the normal human cells and tissues, including T cells, monocytes, macrophages, dentritic cells, natural killer cells (NK) and spleen, lung, prostate but not in the brain, testis or liver. The physiological role of TRAIL is thought to be the control of autoreactive immune cells and immune surveillance, particulary against tumor development and metastasis. Recent evidence indicates that TRAIL may modulate inflammatory responses and collagen expression in fibroblasts, suggesting a potencial role in wound repair, but the most important biological function of this cytokine is inducing apoptosis in cancer, transformed cells with little or no cytotoxity against non-transformed cells and tissues. And thus TRAIL is promising anticancer cytokine [1,8,9,10].

TRAIL-INDUCED APOPTOSIS

TRAIL induces apoptosis in a variety of transformed or tumor cells but not normal cells, making it an attractive agent for cancer therapy. TRAIL induces programmed cell death through interacting with its receptors. There are five TRAIL receptors, including TRAIL-R1 (DR4), TRAIL-R2 (DR5), TRAIL-R3 (DcR1), TRAIL-R4 (DcR2) and osteoprotegerin (OPG). TRAIL-R1 and TRAIL-R2 are the most recently indentified death receptors. TRAIL-R1 receptor is a 445 amino acid type I transmembrane protein. This protein has three cysteine-rich repeats in the extracellular domain, derived from the N-terminus of the protein. Like TRAIL-R1, TRAIL-R2 is also a type I transmembrane protein and consists of 411 amino acids, which includes a 51 amino acid-long signal peptide. Both DR4 and DR5 contain intracellular conserved death domain (DD) motif and have been shown to form both homomeric and heteromeric complexes. Upon binding of TRAIL

trimer, DR4 and/or DR5 are oligomerized and can then transduce the apoptotic signal. Expression of DR4 or DR5 is frequently detected in human cancers cells, such as colon, gastric, ovarian, breast with low or no expression in normal tissues [10,11,12].

By contrast, two membrane – bound decoy receptors called TRAIL-R3 (DcR1) and TRAIL-R4 (DcR2) lack a functional death domain and are unable to activate apoptotic signaling and instead inhibit TRAIL signaling. DcR1 is a glycosylphosphatidylinositol (GPI)-anchored cell surface protein, whereas DcR2 has truncated death domain. The fifth TRAIL-binding receptor is osteoprotegerin, which is a soluble protein that may also function as a decoy receptor by sequestering TRAIL extracellularly. Osteoprotegerin has a low affinity for TRAIL ligand at physiological temperature. On the other hand a recent study suggested that cancer-derivated OPG may be important survival factor in hormone-resistant prostate cancer cells. Decoy receptors modulate the sensitivity of normal and neoplastic cells to TRAIL-induces cytotoxity. The balance of the expression levels between the death receptors and decoy receptors is important factor determining the apoptotic effect of TRAIL. Genes encoding TRAIL-1, 2, 3, 4 receptors are located on human chromosome 8p21-22, what explain their common origin and homology of structure. The gene encoding osteoprotegerin is located on chromosome 8q24 [11,12,13,14,15,16,17].

MECHANISMS OF TRAIL RESISTANCE

TRAIL induces apoptosis in several tumor cell lines, but in non-toxic to normal cells, particularly in its zinc-optimized, soluble trimeric form, but many primary tumors are resistant to TRAIL-induced apoptosis. Upon to half of tumor cell lines may be resistant and several mechanisms underlying TRAIL resistance have been proposed. For example, TRAIL sensitivity may be dependent on the levels of TRAIL receptors. Therefore, the decoy receptors TRAIL-R3 and TRAIL-R4 were initially proposed to negatively regulate TRAIL signaling by competing with TRAIL death receptors for TRAIL binding. The lack of expression of DcRs due to epigenetic silencing correlated with resistance to TRAIL-induced aopotosis in many tumor cell lines. Most recently it was proposed that ratio of TRAIL-R1 to TRAIL-R3 and TRAIL-R4 predicted the sensitivity of tumor cells to TRAIL-mediated apoptosis. Additionally, the authors suggested that distribution of receptors for TRAIL between the cytoplasm and the cell surface as a potential regulatory mechanism. One of the most important TRAIL resistance factor is mutation on death receptor gene and defects in death domain structure. Mutation resulting in loss-of-function of DR4 and DR5-receptors became unable to signaling apoptosis. Such mutans retain their ability to bind ligand TRAIL, lack the capacity to form a functional death-inducing *signaling complex (*DISC). Mutations of the TRAIL-R2 gene have been identified in head and neck cancer, breast cancer and hepatocellular carcinoma [2,4,18,19].

The second group of resistance mechanisms includes anti-apoptotic factors (reduce caspase expression, increase expression of caspase inhibitors such as XIAP, cIAP2, survivin protein, overexpression of Bcl-2 and other inhibiotors of the mitochondrial apoptosis pathway, overexpression cFLIP protein-competitive inhibiotor of caspase-8, defective release Smac/DIABLO from mitochondria, high activity of endothelial nitric oxide synthase (eNOS) and nitric oxide (NO). One of the most important factor caused TRAIL-resistance is expression of NFκB, which has been reported to induce expression of cFLIP, Bcl family members and XIAP. Additional cell survival promoting pathways are likely to influence susceptibility to TRAIL-induced apoptosis. The tumor suppressor p53 upregulates DR5 expression, thereby sentisizing to TRAIL. At last, Six-1 protein expression is very common TRAIL resistance mechanism in advanced metastatic cancers. In summary, a balance between pro - and antiapoptotic factors that exist at the cell-surface and within the cell determines susceptibility to TRAIL-induced death [2,4,20,22,25].

MODULATION OF SENSITIVITY TO TRAIL

A bewildering array of drugs can synergize with TRAIL and have often suggested to provide a useful way to sentitize TRAIL-resistant tumor cells. Thus, scientists are currently attempting to identity TRAIL sensitizers that are able to overcome TRAIL resistance in cancer cells. The chemotherapy agents that are capable of enhancing TRAIL-mediated apoptosis include the most current clinically used drugs, such as cisplatin, taxol, adriamycin, etoposide, 5-FU, carboplatin, paclitaxel [19,23]. Mecha-

nisms of the enhanced interaction between death receptor-mediated signaling transduction and chemotherapy-agent-induced cell death are not fully understood. One possible mechanism for this phenomenon is inducing the expression of TRAIL death receptor-TRAIL-R1 and/or TRAIL-R2 [10,19,23]. Other agents that can promote TRAIL sensitivity in tumor cells include: Smac mimetics, proteasome inhibitors, histone deacetylase inhibitors (HDI), methylation inhibitors. Similar to histone deacetylase inhibitors (HDAC) like trichostatin A and sodium butyrate to sensitize a variety of tumor cells to TRAIL through surface expression of DRs, drugs such as sulphoraphane and curcumin have been reported to enhances sensitivity hepatoma and renal cancer. Proteasome inhibitors such as bortezomib, MG132 can induce expression of death receptors and cause activation of intrinsic apoptotic pathway [2,3,21,22]. Researches reported that combination irradiation with TRAIL protein can upmodulate programmed cell death. This process is regulated by induction of DR4 expression and high activity of caspase 8 [26].
In addition to the induction of apoptosis by this cytokine, several mechanisms have indicated that endogenous TRAIL is important in chemotherapy-induced death. Authors suggested that retinoic acid can induce TRAIL protein expression. Other studies have shown that histone deacetylase inhibitors, DNA metyltransferase inhibitors, TNFα, flavonoids (genistein, kaempferol, quercetin) can upregulate TRAIL expression. In addition, genistein inhibits tumor cell proliferation, induces tumor cell differentiation, triggers cell cycle arrest and apoptosis in some cell types. Treatment with kaempferol is also shown to downregulate XIAP and Bcl-2 family members. Others factors like small molecule XIAP inhibitors can enhance TRAIL sensitivity in tumor cells by inhibiting activity of antiapoptotic proteins. This mechanism was observed in breast cancer, pancreatic cancer, melanoma and leukemia. Interestingly, down-regulation of cFLIP by TRAIL sensitizing drugs was shown to involve different mechanisms [18,20,24,27,30].

INTERFERONS UPREGULATE TRAIL SENSITIVITY IN CELLS

Inteferons (IFNs) are a family of pleiotropic cytokines, which consist of type I (predominantly α and β) and type II (γ). They play an essential role in host defense, having both anti-viral and anti-tumor effects. Recent work demonstrates that IFNs can act as apoptosis-inducing cytokines on various cancer cells, though inducing TRAIL protein expression and inhibiting antiapoptotic protein XIAP. Authors reported that inflammatory stimuli like lipopolysaccharide (LPS) and interferon gamma (IFNγ) upregulate TRAIL protein and mRNA expression in monocytes, macrophages, dendritic cells and NK cells[28; 29]. The same effects was observed using interleukin 2 and 15 (IL-2, IL-15) on NK cells and IL-2 with phutohemagglutinin on lymphocytes surface [5].

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