International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Review Article

ROLE OF TRAIL RECEPTORS ON CANCER

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ABSTRACT

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induces apoptosis in cancer cells without toxicity to normal cells. TRAIL binds to death receptors, TRAIL-R1 (DR4) and TRAIL-R2 (DR5) expressed on cancer cell surface and activates apoptotic pathways. Endogenous TRAIL plays an important role in immune surveillance and defense against cancer cells. However, as more tumor cells are reported to be resistant to TRAIL mediated death, it is important to search for and develop new strategies to overcome this resistance. Since its identification in 1995, TRAIL (TNF-Related Apoptosis Inducing Ligand) has sparked growing interest in oncology due to its reported ability to selectively trigger cancer cell death. Contrary to other members of the TNF superfamily, TRAIL administration *in vivo* is harmless. The relative absence of toxic side effects of this naturally occurring cytokine in addition to its antitumoral properties has led to its preclinical evaluation. However, despite intensive investigations, little is known with regard to the mechanisms underlying TRAIL selectivity or efficiency. Appropriate understanding of its physiological relevance, regulatory pathways and of the mechanisms controlling cancer cells escape to TRAIL-induced cell death will be required to optimally use the cytokine in clinics. The current review focuses on recent advances in the understanding of TRAIL signal transduction and discusses the current and future challenges of TRAIL-based cancer therapy development.

INTRODUCTION

Generally, in normal tissues, a tight balance exists between self-renewal and cell death, and it aims to maintain the tissues' integrity. Once this balance is broken, cells might grow out of control and exhibit resistance to cell death. Uncontrolled growth and apoptosis resistance are two critical hallmarks for cancer initiation as well as progression1 therefore, therapies targeting these two important aspects might be ideal modalities for cancer treatment. Furthermore, in comparison to proliferation inhibition, which only stops tumor growth without removing cancer cells, apoptosis induction might be a more potent therapy because it is also able to completely eliminate the cancer cells that have accumulated diverse mutations over a period of time.

There are two major pathways involved in the process of apoptosis: the intrinsic and extrinsic. The intrinsic pathway depends on mitochondria2 it can eliminate damaged cells via sensing cell damage such as oxidative stress and DNA damage.3 The tumor-suppressor protein p53 is critical in this pathway, as many intrinsic pathways are dependent on this molecule. Thus, p53 is considered as a potential target for cancer therapy. However, mutation or inactivation of p53 is commonly found in tumor cells, leading to the development of resistance to p53-dependent radio- and chemotherapy.4 The extrinsic apoptosis pathway is dependent on death ligands binding to the death receptors (DRs). With ligand engagement to the transmembrane receptors, a death signal is transmitted from the outside to the inside of cells. The first cell death ligand used for anticancer treatment was tumor necrosis factor (TNF), which was discovered in 1975.5 Although TNF showed apoptotic effect in some cancer types, its major function was later found to be involved in the pro-inflammatory process. Subsequently, the DR FAS/APO-1 (CD95) was found to be another anticancer target since antibodies targeting this receptor were able to induce apoptosis in a wide range of cancer cells.6,7 However, stimulation of CD95 also showed acute and lethal hepatic toxicity during its anticancer therapy.8 A few years later, TNF-related apoptosis-inducing ligand (TRAIL) was identified based on its sequence homology to TNF and CD95L.9,10 TRAIL has similar apoptotic effects as CD95L, but it does not affect normal cells,11,12 which makes TRAIL a promising therapeutic for cancer therapy.

There are five types of TRAIL receptors. They are four-membrane receptors TRAIL-R1 (DR4), TRAIL-R2 (DR5), TRAIL-R3 (DcR1), and TRAIL-R4 (DcR1), and one soluble receptor called osteoprotegerin. Among them, TRAIL-R1 (DR4) and TRAIL-R2 (DR5) mediate the apoptosis pathway, and hence are termed DRs, while the others protect cells from apoptosis, and are called decoy receptors (DcRs). With ligand binding to the DR, TRAIL apoptotic signaling is initiated and further induces caspases or mitochondrial-dependent death. Various agents such as recombinant human soluble TRAIL and selective agonistic antibodies targeting TRAIL-R have been developed. Their robust antitumor activities have been demonstrated in a number of preclinical studies. However, subsequent clinical trials revealed only limited therapeutic benefit. This sobering performance might be due to the resistance to TRAIL therapy in most primary cancer cells, since major cell survival signaling cascades including nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and phosphatidylinositol-3-kinases (PI3K/AKT) could also be activated by TRAIL. Therefore,

besides the TRAIL apoptotic signaling pathway, this review also describes the nonapoptotic signaling pathways that can be induced upon TRAIL treatment. An update on the potential anticancer effects of TRAIL in both preclinical and clinical studies is also summarized in this review. The role of few selected, natural compounds that can sensitize tumor cells to TRAIL treatment has been also highlighted briefly

TRAIL-induced apoptosis activation depends on its binding to a TRAIL-R receptor. There are five types of TRAIL receptors: TRAIL-R1 (DR4), TRAIL-R2 (DR-5), TRAILR3 (DcR1), TRAIL-R4 (DcR2) and osteoprotegerin (OPG). TRAIL-R1 and TRAIL-R2 contain a cytoplasmic death domain and transduce apoptotic signals, while TRAIL-R3 and TRAIL-R4, as well as OPG, lack the intracellular death domain and apoptosis-inducing capability and have been proposed to function as decoy receptors, protecting normal cells from apoptosis. TRAIL induces the formation of a pro-apoptotic death-inducing signaling complex (DISC) via its death receptors. The formation of the DISC activates caspase-8, which requires further signal amplification through the mitochondrial pathway for efficient activation of effector caspases in malignant cells 13,14.

Both the pro-apoptotic ligands TRAIL-R1 and TRAIL-R2 may occur also in a soluble form (sTRAIL-R) as a result of exfoliation of this molecule from the cell surface15,16

DISCUSSION

TRAIL is an apoptotic molecule which is usually present in normal environment . However in cancer, there is downregulation of TRAIL ligand and overexpression of TRAIL receptor. Overcoming tumor resistance is the key to success of development of TRAIL receptor targeted therapies for cancer treatment.TRAIL is an important component of the immune defense and powerful inducer of apoptosis in cancer cells by binding with the cell surface death receptors DR4 and DR5. Active avoidance of apoptosis promoting cancer cells survival is one of the hallmarks of tumor development. Many type of cancer cell lines are TRAIL-resistant.TRAIL-induced apoptosis has been shown to be enhanced by combination treatment with radiotherapy and chemotherapy.

CONCLUSION

It has been 20 years since Wiley and colleagues and Pitti and colleagues first described TRAIL (Wiley et al., 1999; Pitti et al., 1996). Over the subsequent two decades, investigation into the natural function of TRAIL in a broad range of diseases and therapeutic potential of TRAIL receptor agonists has yielded a bountiful amount of useful data. While many once viewed TRAIL as that “magic bullet” for treating cancer, it is clear this initial rosy perception has darkened with the underwhelming clinical data exploring TRAIL receptor agonists against cancer. However, hope should not be lost as exciting work continues to be published keeping TRAIL-based cancer immunotherapy a viable future goal. The identification of new drugs that sensitize tumor cells to TRAIL receptor agonists, as well as continued testing of TRAIL receptor agonists with approved drugs, is opening new doors for the treatment of tumors. Caution must be maintained,

however, to limit any potential augmentation in TRAIL sensitivity in normal cells and tissues.

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