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Review Article

Tumor necrosis factor-related apoptosis-inducing ligand polymorphism.

Tamer Mohammed Abdel-lateef Soliman[1], Osama Bakr Seddek[2], Shaimaa Abd EL-Kareem Mohammed[1], Ahmed Sedky Mahmoud[1].

1. Department of Clinical and Chemical Pathology- Faculty of medicine – Sohag University
2. Department of Clinical and Chemical Pathology-faculty of medicine-Assuit University.

Abstract:

TNF superfamily member (TRAIL) is a type II transmembrane protein and is responsible for initiating apoptosis. Macrophages, natural killer (NK), dendritic cells (DCs) and T cells all have TRAIL on their outer surfaces. Like other cytokines, the mature released protein lacks the signal sequence that is present in its pro-form. TRAIL can either be secreted as a dissolved protein or hydrophobic amino acids can attach it to the membrane. Both kinds can act as trimesters and initiate cell death.

Abbreviations: TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand, NK: Natural killer, DC: dendritic cells, IFN: interferon, DISC: death inducing signaling complex.

Keywords: Function of TRAIL, DISC, FADD.

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*Correspondence : sakma201016@gmail.com

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Introduction:

TNF superfamily member (TRAIL) is a type II trans membrane protein and is responsible for initiating apoptosis. [1]Macrophages, natural killer (NK), dendritic cells (DCs) and T cells all have TRAIL on their outer surfaces. Like other cytokines, the mature released protein lacks the signal sequence that is present in its pro-form. TRAIL can be either hydrophobic amino acid-attached to the membrane or secreted as a dissolved protein. The two types can act as trimesters and trigger cell death.[2] TRAIL promotes cell death by attaching to and activating trimeric death receptor. TRAIL is able to connect to five different receptors. DcR1 (TRAILR3) and DcR2 (TRAILR4), two membrane-bound decoy receptors, can't start signals that promote cell death and prevent TRAIL activation, however DR4 and DR5 are both able to signal apoptosis. The 5th TRAIL-binding receptor is osteo protogerin, a soluble protein that has the potential to serve as an inhibitor or decoy by trapping TRAIL extracellularly. [3]

Endogenous TRAIL Secretion and Expression:

TRAIL's primary function is to modulate immune responses as it is expressed on a wide range of immune cells, including monocytes, T cells, NK cells, and DCs. [4] TRAIL is essential for NK cells' capacity to inhibit tumor cell growth and stop metastasis. [5] DC subsets of various types express TRAIL. DCs that have been activated by interferon (IFN) generate TRAIL on their surface, that is thought to be implicated in the cytotoxicity of cancer cells. [6] Only monocytes or T cells that have been exposed to IFN- α or IFN- β may display TRAIL on the surface. [7]

Function of TRAIL:

In response to cytokines, immune effector cells such as NK cells, macrophages, DC, and T cells generate TRAIL on their surfaces, especially IFN-

γ, which contains a reaction component of the promoter of the TRAIL gene. Studies show that TRAIL on NK and T cells is critical for viral infection prevention and tumor immune surveillance.[8] In addition to its function in removing pathogens and choosing the T-cell repertoire, apoptosis also helps to maintain peripheral tolerance.[8] When it comes to cancer, TRAIL signaling is essential for tumor surveillance and metastasis inhibition by natural killer and T cells. However, the loss of antigen-presenting cells or p53 does not appear to have an impact on the development of intestinal tumors. Chemical carcinogens and hematological malignancies are more common in animals lacking TRAIL.[9] Clinical evidence has also revealed that TRAIL may have a role in immunological diseases because people with multiple sclerosis or lupus erythromatosis had greater blood concentrations of dissolved TRAIL. Additionally, TRAIL was connected to cardiovascular conditions including diabetes and atherosclerosis. [10]

Mechanism of TRAIL Signaling Pathway:

When TRAIL or the agonistic DR5 and DR4 antibodies connect to DR4 or DR5, activating DR4 or DR5, the death inducing signaling complex (DISC) is produced. Fas associated death domain (FADD) is an adaptor protein in the DISC directly binds to receptors' intracellular death domain. (Figure1).[8] The concomitant binding of FADD and activation of caspase 8 inactive pro-form most likely results from dimerization. As a result, effector caspases are activated, which degrade cellular proteins and cause apoptosis. [11]

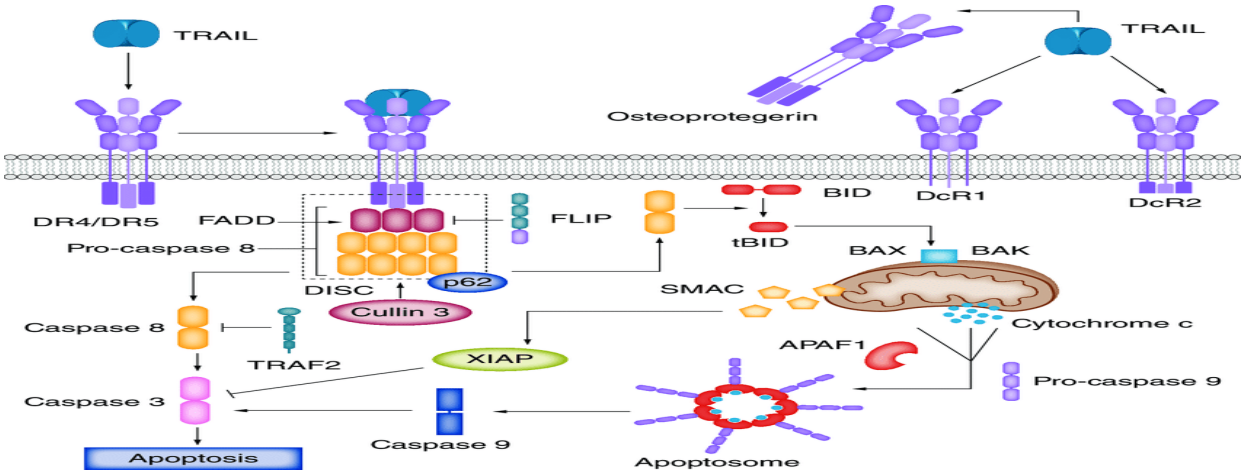

Figure (1). Apoptotic pathway triggered by TRAIL.[12]

TRAIL Signaling Inhibition:

There are various ways to deactivate TRAIL route. Several of these processes exist in cancer cells and aid in the reduction of TRAIL-induced apoptosis sensitivity in those cells. These mechanisms could lower the efficacy of medicines that aim to inhibit surveillance of the host tumor and control of metastasis and to block the TRAIL receptor. [13]Mammalian cells also express DcR1 and DcR2 non-signaling receptors in addition to DR5 and DR4. It was considered that these receptors, which either completely or mostly lack the internal death domain, function as simple decoys by competing for ligand interaction with DR5 and DR4. However, further studies suggest that DcR2 and DcR1 interfere with activation in various ways. In contrast to DcR2-dependent suppression, which includes the creation of heterologous compounds with DR5, DcR1 functions by gradually removing the ligand. [14]One more method to stop it is increased production of FLIP and other TRAIL signaling inhibitors. Because of alterations in the catalytic domain, FLIP, a homolog of Caspase-8, cannot be activated as a protease. [15]

TRAIL protect against diabetes:

Over the past 20 years, multiple research teams examined TRAIL's pleiotropic functions in a variety of illnesses in addition to cancer. Based on increasing scientific and clinical proof that the

TRAIL system is crucial to the onset and progression of both type 1 and type 2 diabetes mellitus, there is an increasing interest in utilizing TRAIL's potential to treat metabolic diseases. (16) Numerous findings from both human and animal studies indicate the association between TRAIL and diabetes, including:

(i) T1DM and T2DM onset and severity can be increased and made worse by TRAIL blocking or inherited deficits.

(ii) Recombinant TRAIL treatment or systemic TRAIL transmission of genes can effectively treat and prevent T1DM and T2DM.

(iii) Diabetes-related macro- and micro vascular issues, as well as T1DM and T2DM patients, all showed significantly reduced levels of circulating dissolved TRAIL.

(iv) Type 2 diabetic patients have a progressive increase in serum TRAIL levels as a result of the action of their anti-diabetic drugs. (17)

The positive effect of TRAIL on homeostasis of adipose tissue suggests a preventative advantage versus obesity, that is strongly related to T2DM. (18)

Conclusion:

TRAIL belong to the TNF superfamily. TRAIL has important function in prevention of viral infections, apoptosis and tumor immune surveillance. TRAIL has been linked to cardiovascular diseases including atherosclerosis and diabetes. Moreover TRAIL has a significant role in protection against diabetes.

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