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A Review

'TRAIL' of targeted colorectal cancer therapy

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TRAIL, a tumor necrosis factor-related apoptosis-inducing ligand is a member of the tumor necrosis factor (TNF) superfamily, which is a cytokine that has shown a particularly precise and selective affinity towards death receptors that are overexpressed in cancer cells. While leaving the normal cells intact and unharmed, due to this property it has been the ligand of choice for highly precise cancer chemotherapeutic delivery system development. On numerous occasions, TRAIL has been used singularly and in combination with other drugs. It was observed that TRAIL had a tendency to be susceptible in terms of the cancer cells developing resistance against it. So TRAIL monotherapy was a bit of a rough patch for the molecule to become successful in the chemotherapy universe, however the conjugations and synergistic actions of TRAIL opened up new horizons which are discussed in this review with specific interest on colorectal cancer (CRC).

Keywords: Adenosquamous, Apoptosis, Capsazepine, Carcinoma, Doxorubicin, Necrosis, Protein kinase

Introduction

Despite many efforts and achievements, the tumor is infamous for returning and developing resilience to treatments. Huge efforts are being made in this area to create new strategies that will boost precise targeting and overcome the tumors' mechanism of resistance to existing treatments[1]. According to statistics, colon cancer (CRC) is the third most common carcinoma to be newly diagnosed worldwide and the top cause of mortality in America. Adenocarcinoma is the most common diagnosis for CRCs, accounting for nearly 90% of all instances that have been documented[2]. Adenosquamous carcinoma, spindle cell carcinoma, squamous cell carcinoma, and undifferentiated carcinoma are a few additional uncommon diagnoses.In 1946, William Coley discovered that certain sarcomas shrank in size in response to bacterial infections. This resulted in the first identification of tumor necrosis factor (TNF).Studies on this protein inspired the search for related compounds and the possible identification of TNF as a target to trigger apoptosis. The testing of molecules like CD95 for systemic application was abruptly stopped due to serious hepatotoxicity that had been documented[3]. Yet another TNF super family (TNFSF) member, known as Tumor Necrosis Factor Related Apoptosis Inducing Ligand (TRAIL, also known as Apo2L or TNFSF10), demonstrated highly selective apoptotic cell death induction in tumor tissues without having negative effects on normal cells, unlike its forerunners, TNF or CD95 agonists. As the saying goes, "third time's a charm." [4] Here in this review we have summarized the use of TRAIL as a targeting ligand, what was the past, present, and future of this targeted cancer chemotherapy and how nanotechnology can improve the chances in the disease [5]

Colorectal cancer epidemiology

Almost 10% of all diagnosed carcinomas are blamed on CRC. According to GLOBOCAN20, CRC is the third most often diagnosed cancer overall, behind lung and liver cancer in both males and females, and only behind breast cancer. However, mortality among all carcinomas in both males and females is in the 12-13% range, with mortality in females being about 19% lower than in males[6].

Pathogenesis of colorectal cancer

The majority of CRCs are thought to have developed from stem cells or cells that resemble stem cells. cancer stem cells, which are visible at the base of the crypts developed in the wall of the intestine, are produced as a result of an accumulation of genetic and

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epigenetic chromosomal abnormalities. They are responsible for the development, upkeep, and progression of malignancies[7,8]. The majority of CRCs (70–90%) grow by an adenoma-carcinoma route, but the remaining 10–20% have demonstrated to originate through a serrated neoplasia journey, which has unique genetic and epigenetic variables and stages in a sequential manner. Tumor microenvironment (TME) consists mostly of recruited immune cells and the nervous system. The interactions between TME and tumorigenesis has been recently well established, Chronic inflammation[9] leads to DNA damage, epigenetic changes and replication induced stress on the epithelial tissue, this helps in tumorigenesis, after the tumor has progressed to a certain extent, tumor elicits inflammatory response by structural damage to intestinal barrier exposing it to other toxins and DNA damage caused by factors released by microbial growth after the protective barrier is lost. Growth of the tumor also leads to hypoxic conduction which have been shown to be one of the major cause of oxidative stress related further damage to DNA[10]. Apart from this, the recruitment and differentiation of T regulatory cells in the TME helps the tumor to attain immuno-resistance, this helps in progression and promotion of CRC. Over expression of genes that lead to nuclear factor κB and STAT3 transcription pathway and silencing of tumor suppressor genes that control the expression of DNA methyl transferases like DNMT1 and DNMT3 plays important role in the development and progression of CRC [11]

TRAIL: The origin and Mechanism in CRC

TRAIL, also known as Apo2 ligand or Apo2L or TNF- related apoptosis inducing ligand, was initially identified as a chemical that may cause apoptosis without the help of the Fas (Apo1 receptor of the TNF family).TRAIL is a type 2 transmembrane protein with a calculated molecular mass of 32.5 kDa and 281 amino acids. However, when the moiety is complete and entirely glycosylated, the anticipated molecular mass is 41 kDa.TRAIL is different from the other TNFSF members in that it has five targets, four of which are surface and one of them is soluble. DR4/TRAIL-R1, DR5/TRAIL-R2, DcR1/TRAIL-R3,[12,13] and TRAIL-R4/DcR2 are their respective designations. In addition to all these four, a fifth soluble TRAIL receptor known as osteoprotegerin was discovered in the late 1990s[14,15].

TRAIL- conjugated engineered drug delivery systems for CRC

The TRAIL drug delivery system was created by formulators to tackle the two primary challenges of (I) decreased stability and (II) less accumulation in death receptors. To address these issues, valency with stabilization and conjugations to boost precision in cancer targeting were modified. the development of many similar formulas were carried out conjugating TRAIL with current anticancer chemotherapeutic agents, biological agents such as anti-VEGF antibodies and phytoconstituents like cannabidiol, diallyl di sulfate etc[16].

TRAIL formulations for targeted CRC treatment

The conjugation of TRAIL or TRAIL-R antibodies with chemotherapy agents in a nanoparticle - based format ushered in a new era of bullseye cancer treatment for various malignancies because chemotherapeutic drugs increased TRAIL sensitization in malignant cells where the TRAIL provided the agents with a specified target. Active targeting, in which biomoleculefragments are used to direct TRAIL toward a particular tumor by using the surface molecules as antigens, and passive targeting based on the enhanced permeability and retention (EPR) effect have been the two main targeting strategies pursued in this particular instance.

Active targeting of CRC using TRAIL

Numerous conjugations and modifications using other molecules to direct TRAIL towards specific death receptors so it can elicit apoptotic activity in the target CRC tissue[17], TRAIL with miRNA-128, CRC cells often protect themselves by reducing reactive oxygen species (ROS) stress by depleting itself of miRNA128, combination of TRAIL with the former gives the delivery system an edge of hyper-burdening the CRC tissue with ROS, in turn increasing the death receptors therefore sensitizing the tissue to higher action of TRAIL. Such mechanisms are also employed in delivery system of TRAIL combining it with Amuc_14364* that sensitizes CRC tissue by degrading protective mucin cover around them, delivery systems like microspheres, immunoliposomes, lipid bilayer liposomes, and fusion proteins containing drugs like heparin, antibodies and doxorubicin have been popularly used to target and deliver TRAIL to CRC cells[18–20].

Passive Targeting of TRAIL

Passive targeting has always been the delivery mechanism of choice for TRAIL, due to reasons like, a) TRAIL resistance is a challenging hurdle in active targeting, b) passive targeting enables the delivery system to have a double pronged attack of synergism as the drug of choice and TRAIL both have anti-cancer activity, c) given the selective nature of TRAIL it can actually act as a targeting moiety as well as a chemotherapeutic agent. TRAIL in conjugation and form of iron oxide nanoclusters, combined with RUNT related transcription factor[21], mitogen induced protein kinase enzymes, and farnesoid X receptor agonists, all showed promising action of TRAIL along with the drugs. As they improve their own potential anticancer activity along with the one of TRAIL[22].

Phytoconstituents such as cannabidiol[23] and Diallyl di sulfate, have been shown to achieve an improved anti-tumor activity when delivered along with TRAIL. Capsazepine in a lipid raft formulation, doxorubicin in polyamido dendrimer formulation, and oncolytic adenovirus gene containing TRAIL code in a targeted adenovirus delivery system have shown particularly high action of apoptosis action in malignant tissues.

Conclusion

As we can see from the studies that have been conducted in past using TRAIL and the combinations, it is safe to state that even though having the hurdles of resistance and poor accumulation at the site of action TRAIL can still be proven as a potent and useful weapon in the targeted therapy of colorectal cancer. The future lies in creating affordable and mass producible TRAIL analogues or antibodies which can be surface coated on nanoparticles carrying various chemotherapeutic agents as well as biological and phytochemical substances. Hybrid drug delivery can be of great use in future for the specific treatment and with the advantage of low dosage requirement and less chances of occurrence of side effects associated with current treatments like oxaliplatin.

Now, we may draw the conclusion which states that it is a topic that have been explored only superficially, there is a more to uncover regarding TRAIL, it's association with death receptors, the delivery system engineering and the future prospect of creating a sensitive, highly precise, low toxic, potent and affordable cancer drug delivery system using TRAIL.

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Conflicts of interest

All authors declare no conflicts of interest.

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