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Review

Therapeutic targeting of the TNF superfamily: A promising treatment for advanced endometrial adenocarcinoma

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HIGHLIGHTS

► Targeting TNF superfamily for endometrial adenocarcinoma treatment.
► Targeting TNFα, NF-κB, FAS and TRAIL pathway.

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ABSTRACT

Surgical treatment including total abdominal hysterectomy + bilateral salpingo oopherectomy (TAH + BSO) with pelvic and para-aortic lymphadenectomy may not be sufficient to treat cases with advanced endometrial adenocarcinoma (EAC), and in these cases, adjuvant treatments including radiotherapy and/or chemotherapy, are employed based upon the tumor location, type and stage of the disease. These treatment modalities have high incidence of systemic toxicity, thereby compelling clinicians to look for targeted therapy aiming specifically at the malignant cells. Bevacizumab (anti-VEGF), temsirolimus (mTOR inhibitor) and aflibercept (VEGF trap) are already under clinical trials in women with EAC. Targeting the ligands and receptors of the tumor necrosis factor (TNF) superfamily holds promise in this regard. The objective of this review is to provide an overview of the various mechanisms and pathways related to the TNF superfamily involved in advanced EAC and to identify the new therapeutic strategies for specifically targeting these impaired pathways. In addition, the development of treatments for EAC is also discussed. The possible therapeutic treatments include targeting TNFα and its receptors using monoclonal antibodies (MAbs) such as infliximab, adalimumab, etanercept, and certolizumab. Proteosome inhibitors including bortezomib and the anti CD-20 agent rituximab are used to inhibit the NF-κB pathway. Other options include targeting the FAS (CD95) pathway and the TNF-related apoptosis-inducing ligand (TRAIL) pathway using agents such as mapatumab, lexatumumab, and conatumumab. These pathways are known to be involved in the pathogenesis of EAC. Moreover, there is adequate evidence to warrant the use of drugs that target the TNF superfamily for the treatment of advanced EAC.

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Introduction

Endometrial adenocarcinoma (EAC) is the most common form of gynecological malignancy in developed countries [1]. It usually occurs in post-menopausal women, although is not uncommon in younger women. While the rate of incidence in the USA is approximately 20 per 100,000 women [1], it varies from 23 in UK to >40 in Czech per 100,000 women in Europe. The commonest presentation is bleeding per vaginum. This symptom in post-menopausal women usually leads to immediate gynecological work-up and diagnosis. Hence, even though it is a very common malignancy, deaths are relatively less common with 5 year survival rates approaching 95%, when detection is during stage I of the disease.

There are two distinct types of EAC including Type I, which accounts for majority of the cases (>80%) and Type II, which is the relatively rare and more aggressive form with p53 and Her2/neu mutations [2,3]. Drugs such as tamoxifen citrate and estrogen hormone replacement therapy are known to increase the risk of Type I EAC [2]. Type II EAC is estrogen independent and more commonly seen in the Black race [4]. Histologically, Type II EAC tends to be a poorly differentiated serous, papillary or clear cell type as opposed to Type I, which is a well-differentiated endometrioid type [2].

The gold standard treatment option for EAC is total abdominal hysterectomy + bilateral salpingo-oopherectomy (TAH + BSO) in conjunction with adjuvant radiotherapy and/or chemotherapy, depending upon the anatomical location of the invasion, type and staging of the disease. Currently, the chemotherapeutic regimes consist of cytotoxic drugs such as cisplatin, doxorubicin and paclitaxel [5]. Although these drugs are effective, they act on the dividing cells of the body thereby causing significant and even life-threatening side effects such as neurotoxicity, arrhythmias, dilated cardiomyopathies, ototoxicity, ovarian damage, and bone marrow suppression leading to associated complications including anemia, neutropenia and thrombocytopenia. This dilemma has led to a search for alternate chemotherapeutic agents which have a more specific mechanism of action and, hence, may be safer than the generic cytotoxic agents presently available.

To circumvent the systemic toxicities associated with conventional chemotherapeutic drugs, great efforts are being put toward the identification of novel anti-cancer agents targeting specific pathways involved in tumorigenesis of various malignancies. New anti-angiogenic agents such as bevacizumab, aflibercept and mTOR inhibitors like temsirolimus are presently under trials for effective therapeutic management of EAC [6–8].

An emerging option for the treatment of EAC is targeting the tumor necrosis factor (TNF) superfamily. This class of ligands and its receptors have generated considerable academic interest ever since the first ligand TNFα was isolated in the 1980s [9]. TNF superfamily, presently consisting of more than 20 ligands and about 30 receptors, has been shown to play a significant role in immunity. Various autoimmune disorders such as Crohn's disease, psoriasis, and rheumatoid arthritis are presently being treated by targeting the TNF family of ligands and receptors [10]. Further, it is well accepted that this class of ligands and receptors is involved in apoptosis, and that cancer cells evade apoptotic pathways.

An extensive literature review shows that a systematic evaluation of treatment options available for advanced endometrial adenocarcinoma by targeting TNF super family of ligands and receptors is lacking. The aim of the present review is to identify the possible therapeutic targets in the TNF superfamily which may be considered for providing an effective treatment option for EAC.

Overview of TNF superfamily

Ligands and receptors

The ligands of the TNF superfamily bind to specific receptors; however, in some cases a ligand can bind to more than one receptor. The key ligands of the TNF superfamily include APRIL, BAFF, CD30L, CD40L, CD70, CD95L, OX40L, LTα, LTβ, RANKL, TNFα and TRAIL. The receptors for the TNF ligands are transmembrane proteins which act through cytoplasmic signaling pathways. Based upon these pathways, the TNF receptors are classified into three main groups [11]:

1) Group containing the death domain (DD) receptors—activation of these receptors leads to apoptosis of the cell. Some examples include CD95, DR3, DR4, DR5, DR6 and TNFR1.
2) Group of receptors activating the nuclear factor-κB (NF-κB), Jun N-terminal kinase (JNK), p38, extracellular signal regulated kinase (ERK) and phosphoinisitide-3 kinase (PI-3 K). Some examples include CD27, CD30, CD40, LTβR, OX40 and RANK.
3) Group with receptors having no known intracellular pathways. Examples include DcR1, DcR2, DcR3 and OPG. These are also known as decoy receptors which competitively inhibit other receptor groups.

Ligands including TNFα, TRAIL and CD95L are capable of binding to the first group of receptors thereby activating the cell apoptosis pathways. Initiation of the apoptosis pathway in this case usually occurs by the activation of caspases. This pathway is called the extrinsic apoptotic pathway. For example, binding of the CD95 receptor or TRAIL receptor activates the caspase 8 initiator which, in turn, activates caspase 3, resulting in cell death [12,13]. Conventional chemotherapy and radiotherapy induce apoptosis via both the mitochondrial p53 pathway (intrinsic) and extrinsic apoptotic pathway, thereby increasing systemic toxicity [12,13].

Over the last few years, a myriad of interconnected intracellular pathways involving the TNF family has been discovered which are being tested in cancer therapy. These discoveries and initial successes in the treatment of other cancers [14] usher in a promise for the treatment of EAC by targeting the TNF superfamily.

Targeting the TNF superfamily

TNFα

TNFα binds to the receptors TNF-R1 and TNF-R2 and initiates both pro-apoptotic and anti-apoptotic signaling cascades. Although TNFα was known to be a powerful anti-tumor agent when it was first discovered, it was quickly established to have tumorigenic properties including initiation, angiogenesis and metastasis, largely through the activation of NF-κB and MAPK pathways [15]. In view of the fact that it has both pro- and anti-apoptotic activity, it is crucial to understand the intricate pathways and molecular interplay involving TNFα before arriving at a suitable treatment option.

Vaskivuo et al. observed TNFα to be down-regulated in EAC [16]. The cytokine shows anti-tumor activity when administered through