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Efficacy of Apoptic Agents in Cervical Cancer Treatment

Servikal Kanser Tedavisinde Apopitotik Ajanların Etkinliği

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ABSTRACT

Cervical cancer is one of the prevalent gynecologic cancer in the world. Through the cancer development mechanism, it is well known that apoptosis is so important. Many of the studies investigate the relation between apoptosis and carcinogenesis and related to this treatment regimen also. In this review, we aimed to analyse new opportunities in cervical cancer treatment, in the light of the literature.

Keywords: Cervical cancer, apoptosis, targeted therapy

ÖZ

Serviks kanseri en sık görülen jinekolojik kanserlerden biridir. Kanser gelişim mekanizmasında apopitozisin önemi bilinmektedir. Birçok çalışmada apopitozisin karsinogenezle ilişkisi ve buna bağlı olarak tedavi rejimleri araştırılmaktadır. Bu derlemede; literatür ışığında servikal kanser tedavisi alanında yeni seçenekleri araştırmayı hedefledik.

Anahtar Sözcükler: Servikal kanser, apopitozis, hedeflenmiş tedavi

INTRODUCTION

Cervical cancer is the second most prevalent cancer among women and the fourth leading cause of gynecological cancer-associated deaths globally, with around 660,000 new cases and 350,000 deaths in 2022 (1). Unfortunately, in developing countries that do not have cervical cancer screening and prevention programs, cervical cancer remains the most common gynaecologic cancer (17.8 per 100,000 women), and leading cause of cancer deaths (9.8 per 100,000) among all types of cancer in women (2). Despite this being one of the most preventable and treatable forms of cancer, it is crucial that it is detected early and managed effectively. The primary goal of cervical screening is to prevent cervical cancer. This would be achieved by the detection, treatment, and follow-up of preinvasive cervical lesions (3,4)

Essentially all cervical cancers arise from persistent genital human papilloma virus (HPV) infections. It is a classic example of virus-induced carcinogenesis. Persistent sexually transmitted infection with about 15 high-risk human papilloma virus (hr-HPV) types leads to cervical cancer, with HPV-16 and HPV-18 infections accounting for about 70% of the total cases (5,6). According to the 11 case-control studies, HPV types 16, 18, 45, 31, 33, 35, 52, and 58 accounted for 95 percent of the HPV DNA-positive squamous-cell carcinomas (7).

HPV infection leads to cancer through multiple pathways, but interaction of the HPV *E6* and *E7* gene (early gene 6 and 7) products with p53 and *retinoblastoma* gene (pRb) is critical: By inactivating or activating degradation of their targets, *E6* and *E7* gene eliminate genetic surveillance and allow unchecked cell cycling, leading to the accumulation of mutations and eventual invasive cancer. Initial infection in basal epithelial cells leads to establishment of a ring chromosome from which carcinogenic proteins are elaborated while virion production occurs in maturing epithelium. Disruption of the ring, often at the HPV *E2* regulatory region, allows integration of *E6* and *E7* sequences into the host genome. The accumulation of mutations leads to nuclear changes visible cytologically as a high-grade squamous intraepithelial lesion and histologically as

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high-grade cervical intraepithelial neoplasia (CIN). Selection for invasiveness and metastasis through additional mutation and through gene methylation results in the evolution of cancer (8).

E6 increases telomerase activity in keratinocytes through increased transcription of the *telomerase catalytic subunit* gene via induction of c-myc (9,10). E6 mediation of telomerase activity may predispose individuals to long-term infection and the development of cancer (11).

The *E7* gene product is a nuclear phosphoprotein that associates with the product of the *pRb* gene (*pRb*), which is a *tumor suppressor* gene important in the negative control of cell growth (12,13). Degradation of p53 by E6 and the functional inactivation of Rb by E7 represent the main mechanisms whereby expression of HPV E6 and E7 oncoproteins subverts the function of the negative regulators of the cell cycle (14,15). Deregulated expression of the viral oncogenes is a predisposing factor for the development of HPV-associated cancers.

Apoptosis refers to programmed cell death and the "intentional" induction of cell death. Cell death is important in the growth and development of an organism because as an organism matures and differentiates, cells must die to give way to more differentiated and specialized cells (16). If the apoptosis mechanism does not work and a cell becomes immortal, it can result in tumor formation or cancer. In cancer, apoptosis appears to be a mechanism for deleting cells from the population that have sustained carcinogenic DNA damage; however, when genes such as B-cell lymphoma-2 (BCL-2) and Tp53 are involved, these cells are suddenly free to continue replicating and propagating their mutations. This genetic instability may be an early step in the development of cancers. Mutations in BCL2 and Tp53 may then influence the effectiveness of these therapies through their ability to inhibit cell death (17).

Apoptosis is a balance between proliferation and death of the cell. It is critical in mammals because it plays a role in development as well as homeostasis (18). The apoptotic pathway is activated by both intrinsic and extrinsic signals, that are referred to as the mitochondrial and death receptor pathways. The intracellular signals include DNA damage, whereas the most frequent extracellular signals are death-inducing signals produced by cytotoxic T cells from the immune system in response to damaged or infected cells (19). After the signaled apoptosis, changes begin to occur within the cell which include activation of caspases (cysteine aspartyl-specific proteases) that cleave cellular components required for normal cellular function such as cytoskeletal and nuclear proteins. As a result of caspase activity, apoptotic cells begin to undergo plasma membrane changes that signal the macrophage response (20).

The intrinsic pathway is regulated by the BCL-2 protein family that includes proapoptotic effector proteins, proapoptotic BH3-only proteins, and antiapoptotic BCL-2 proteins (21). The antiapoptotic BCL-2 proteins inhibit apoptosis by suppressing the proapoptotic BCL-2 proteins, BCL-2 associated X protein (BAX), and BCL-2 homologous antagonist killer (BAK). BH3-only proteins inhibit the antiapoptotic BCL-2 proteins (19). As a result the imbalance of the apoptosis causes wide variety of diseases.

Cancer and Apoptosis

The hallmarks of cancer are present in all cancer cells regardless of the cause or type; these include uncontrolled growth, angiogenesis, and apoptosis deficiency. The main function of apoptosis is the prevention of cancer (21). According to this approach, targeting apoptosis should maintain effectiveness for all types of cancer treatment. There are many treatment strategies that target various stages in both the intrinsic and extrinsic pathways. Two common strategies for therapeutic targeting are stimulation of proapoptotic molecules and inhibition of antiapoptotic molecules. Anyway, there is no indication of which target is most effective. As more apoptosis-inducing anticancer drugs are designed, the most effective targets will be determined (19,20).

In almost half of all human cancers, BCL-2 expression is elevated. Related to this, the great majority of the anticancer agents depend on BCL-2/BAX-dependent mechanisms to kill cancer cells. If there is a defect in this mechanism, it causes ineffectiveness of drugs. The threshold for chemotherapy or radiotherapy is raised due to apoptosis defects, which lead to resistance to those therapies (18,20).

Intrinsic Pathway of Apoptosis

It depends on mitochondria and mitochondrial proteins. Cells can also activate their apoptosis program from inside the cell, often in response to stresses such as DNA damage or developmental signals. A key protein in the intrinsic pathway is cytochrome c, a water-soluble component of the mitochondrial electron-transport chain (22). When released into the cytosol, it binds to an adaptor protein called apoptotic protease activating factor-1 (Apaf1), causing Apaf1 to oligomerize into a wheel-like heptamer called an apoptosome. Then procaspase-9 is converted into caspase-9 that activates caspases-3 and -7. The executioner caspases immediately begin to break down proteins, leading to cell death (23). The overall pathway is regulated by the proteins of the BCL-2 family, (19). This family controls the release of cytochrome c and other intermembrane mitochondrial proteins into the cytosol. Some BCL-2 family proteins are pro-apoptotic and promote apoptosis by enhancing the release, whereas others are anti-apoptotic and inhibit apoptosis by blocking the release. BAX and BAK are the main effector BCL-2 family proteins; BAK is located in the outer membrane of mitochondria, whereas BAX is in the cytosol and translocates to the mitochondria after the activation of an apoptotic signal. Their activation depends on activated pro-apoptotic BH3-only proteins.

The BH3-only proteins are the largest subclass of BCL-2 family proteins. The cell either produces or activates them in response to an apoptotic stimulus, and they are thought to promote apoptosis mainly by inhibiting anti-apoptotic BCL-2 family proteins.

Extrinsic Pathway of Apoptosis

Extracellular signals such as the tumor necrosis factor and related apoptosis-inducing ligands, fatty acid synthase ligand, as well as other death ligands that interact with cell surface receptors, can induce activation of caspases and lead to apoptosis via an extrinsic pathway (24). Initiator procaspases-8 and -10 bind to the adaptor protein, forming the death-inducing signaling complex (19,25). Executioner caspases 3, 6 and 7 are then activated and begin the cleavage of proteins and the cytoskeleton, leading to cell death (20).

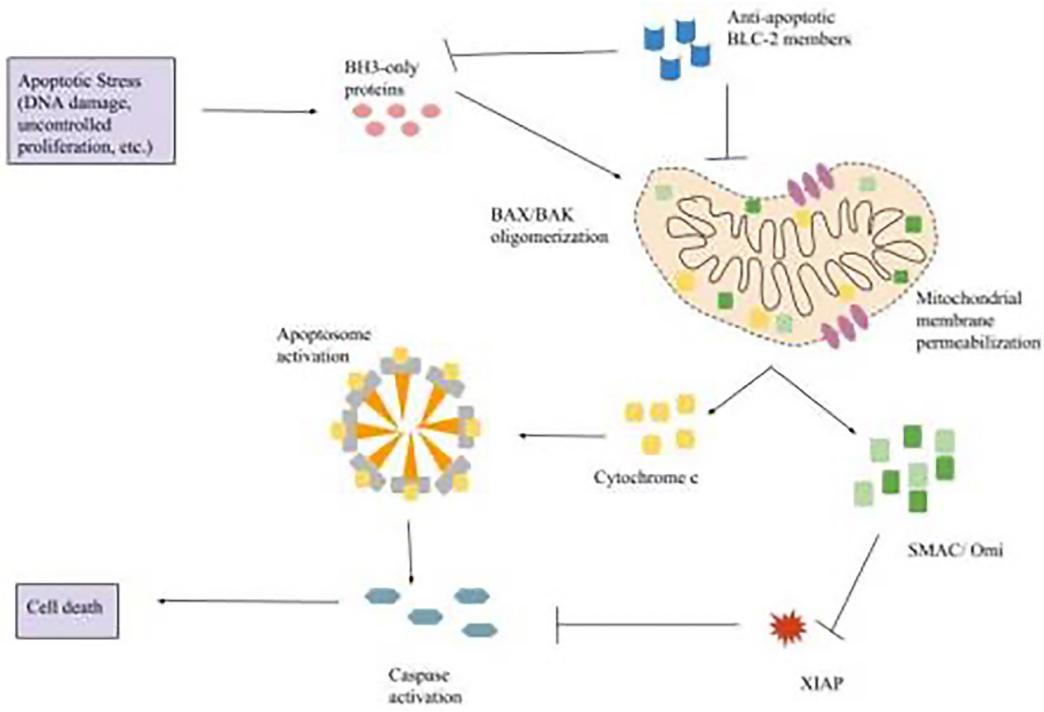

Figure 1. Intrinsic pathway of apoptosis

DNA: Deoxyribonucleic acid, BLC-2: B-cell lymphoma 2, BAX/BAK: BCL-2-associated X protein/ BCL-2 homologous antagonist/killer, SMAC: Second mitochondria-derived activator of caspases, XIAP: X-Linked Inhibitor Of Apoptosis

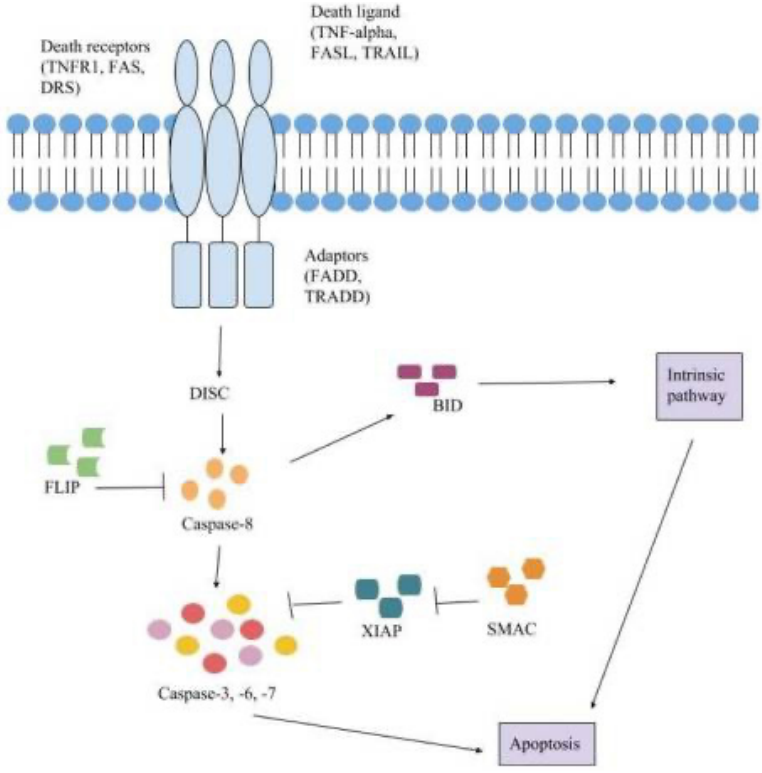

Figure 2. Extrinsic pathway of apoptosis

TNFR1: Tumor necrosis factor receptor 1, FAS: CD95L, DRS: Death receptors, TNF-alpha: Tumor necrosis factor- alpha, FASL: FAS ligand, TRAIL: TNF related apoptosis inducing ligand, FADD: Fas Associated Via Death Domain, TRADD: Tumor necrosis factor receptor type 1-associated DEATH domain protein, DISC: The death-inducing signaling complex, FLIP: FADD-like apoptosis regulator, BID: BH3 interacting-domain, SMAC: Second mitochondria-derived activator of caspases, XIAP: X-Linked Inhibitor Of Apoptosis

Cervical Cancer and Apoptosis

Current cervical cancer treatment depends on the stage of the disease and consists of surgery, radiotherapy, or chemotherapy; treatment resistance, particularly in advanced and recurrent cases of cervical cancer, remains a challenge. A deeper understanding of signaling pathways and gene aberrations in cervical cancer pathogenesis has assisted in identifying potential molecular targets for therapy and has led to the use of targeted therapies for the treatment of cervical cancer either as single agents or in combination with chemotherapeutic drugs. Thus far, bevacizumab and the immune checkpoint inhibitor pembrolizumab (which targets the PD-L1 protein) are the only targeted therapies approved by the US Food and Drug Administration for the treatment of advanced and recurrent cervical cancer. Bevacizumab is used in combination with chemotherapeutic drugs, namely cisplatin, paclitaxel, and carboplatin, to treat patients with advanced and recurrent cervical cancer. Pembrolizumab is used for the treatment of patients diagnosed with advanced recurrent cervical cancer. Approval of targeted therapies for the management of cervical cancer, has opened new treatment avenues for patients who otherwise had limited treatment options once they developed resistance to standard treatment. Targeting the BCL-2 family of proteins with BH3-mimetics for cervical cancer treatment could be a new treatment approach for cervical cancer management (26).

Relationship Between BCL-2 and EF-24

In recent years, there has been a growing tendency toward the use of phytochemicals in plants for the prevention and treatment of human diseases. Several of these phytochemicals have shown potential as cancer chemopreventive or therapeutic agents in the human body (27).

Diphenyldifluoroketone (EF-24), a monoketone analog of curcumin, is efficacious in anticancer screens and has been reported to inhibit the growth of tumor cells. It has anti-inflammatory, antimicrobial, antioxidative, immunomodulating, and anti-atherogenic features. It is suggested that EF-24 induced nuclear condensation and fragmentation , leading to the activation of caspase -3/-7, which triggers apoptosis (28). Yang et al. (27) reported that curcumin or EF-24 treatment decreased the level of BCL-2 but increased the level of BAX. The BAX/BCL-2 ratio is one of the hallmarks of the intrinsic mechanism of apoptosis in the mitochondria. So this medication helps to activate apoptosis in cancer treatment.

Effect of BCL-2 Anti-apoptotic Proteins for Cervical Cancer Progression

The expression of BCL-2 in relation to cervical cancer progression was mainly evaluated by immunohistochemistry (IHC). There were a number of studies which investigated the expression of BCL-2 in different grades of CIN (CIN, there are three CIN grades, namely CIN 1, CIN 2, and CIN 3) lesions and invasive squamous cervical carcinoma tissue sections. Using IHC, expression of BCL-2 was reported to increase with the rising grade of CIN (29,30), although, only one study showed a significant increase of BCL-2 in different CIN grades (29). Contrary to these studies, BCL-2 expression was reported to decrease with increasing grades of CIN in one study. However, there was no significant difference reported (31).

On the other hand, the five-year survival rate in cervical cancer is found positively correlated with BCL-2 expression, and it is especially associated with poor prognosis in metastatic diseases (32,33). Zhu et al. (34) also found that BCL-2-negative status was an independent predictor of pathological complete response in breast cancer patients. However, some trials had drawn different conclusions, suggesting positive BCL-2 may predict a favorable chemotherapeutic effect.

Effect of Apoptotic Proteins for Cervical Cancer Treatment

Treatment of invasive cancer involves appropriate management for both the primary lesion and potential sites of metastatic disease. In early stages (Stage I and IIA), either surgery or radiation therapy are acceptable for primary treatment, whereas chemoradiotherapy is used for advanced stages. However, there is an urgent need for more effective therapies in recurrent/metastatic cervical cancer. Clinical trials have suggested that biologic therapies may be helpful. In the literature, there are numerous studies about several agents in cancer therapies, such as angiogenic inhibitors, apoptotic agents, epidermal growth factor receptor inhibitors, mechanistic target of rapamycin pathway inhibitors, immunotherapy, monoclonal antibodies, poly(ADP-ribose) polymerase inhibitors, and more.

Especially, EF-24 acts more powerful bioactivity for anti-inflammatory and anti-cancer activity. However, the effects and mechanism of EF-24 on cervical cancer have not been fully investigated. Lee et al., evaluated the effects of EF-24 on tissue plasminogen activator (TPA)-induced cellular migration of cervical cancer. According to this article, EF-24 inhibited TPA-induced cellular migration and cellular invasion of cervical cancer cell lines by modulating MMP-9 expression via downregulating the p38 signaling pathway potential to serve as a chemopreventive agent for cervical cancer (35).

In a review, it is emphasized that targeting the apoptotic pathway is an effective option to help treat cancer, but it is necessary to systematically analyze the role of BCL-2 family proteins in regulating apoptosis and cancer treatment. Related to this, if BCL-2 and BCL-XL can be functionally blocked, the apoptosis of tumor cells can be restored. Many members of this family can be used as tumor prognostic genes and have important effects on tumor prevention and treatment (36).

Kaloni et al. (37) signed at the reduction of pro-apoptotic members of the BCL-2 family has also been implicated in the development and therapy resistance of cancer.

According to one randomised controlled trial that includes cervical carcinoma stage IIB-IIIB patients, the group treated with curcumin + radiation showed increased survival rates compared to the group treated with placebo + radiation. As a result, they have reported that curcumin is an effective, alternative radiosensitizer for application in cervical cancer treatment (38).

In addition to this, in Zhang et al. (39) study, it is noted that there is a lack of systematic reviews on the mechanism of action of curcumin against cervical cancer. Because there are few clinical trials of curcumin against cancer, and novel formulations of curcumin still need to be developed the optimal dose of curcumin for cervical cancer needs to be investigated.

CONCLUSION

Targeting the apoptotic pathway is a classic but effective approach to anticancer therapies regardless of cancer type. Because of the apoptosis deficiency, there are various mutations found in both extrinsic and intrinsic pathways in cancer. The efficacy of targeting and activating an apoptotic pathway holds promise for a significant cancer therapy. However, there is a great need to conduct further research in this field.

Footnotes

Authorship Contributions

Concept: E.İ.B., H.İ.Ö., Design: : E.İ.B., Supervision: : E.İ.B., H.İ.Ö., Resources: : E.İ.B., H.İ.Ö., Material: : E.İ.B., H.İ.Ö., Data Collection or Processing: : E.İ.B., Analysis or Interpretation: : E.İ.B., H.İ.Ö., Literature Search: : E.İ.B., H.İ.Ö., Writing: E.İ.B.

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