



RECENT ADVANCES IN TREATMENT OF OVARIAN CANCER

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Summary

Ovarian cancer develops due to abnormal growth of cells and tissues of ovaries. Various types of chemotherapeutic agents are used to treat this dreadful disease. But unfortunately, resistances against various drugs are developed due to their long term use. So, therapy based on various targeted genes, interleukins, and angiogenesis inhibitors are in clinical use now a days.

Keywords: Ovarian cancer, gene therapy, ID1

Introduction

Ovarian cancer develops due to abnormal growth of cells and tissues of ovaries; the component of a female reproductive system. Actually, adult cells don't expire and novel cells also produce even when body doesn't require them and in this way tumor develops. Benign and malignant are the two types of tumor. Benign tumors are non invasive, non metastatic, localized and capsulated, in short, they are less dangerous. Malignant tumors are locally invasive, metastatic, non-localized, non-capsulated i.e. they are more harmful and serious than benign tumor. Mostly, drugs that are given for the treatment of ovarian cancer are 5-fluorocytosine, camptothecin-11, ET-743, PM00104, cisplatin, DNA methylation inhibitors, decitabine (phase 1 trial), Dasatinib, paclitaxel. [1-5]

Several gene therapy policies are in experimental stages found on idea of increase immune reaction in opposition to a cancer, reticence of new blood vessel formation, and development feature. Now a day's non-viral deliverance scheme is considered better than viral delivery system. [6] TP53 and transforming growth factor beta (TGF- β) are considered as basic genes in platinum confrontation in ovarian tumor exposed by explorative alleyway examination. [7]

Possible targets for gene therapy of ovarian cancer

Annexin A3

Ovarian cancer cells due to annexin A3 appearance become more vulnerable to platinum drugs and its appearance is decreased via Annexin A3 antisense, so in this way cancerous cells become more responsive to platinum drugs. So, annexin A3 may be an objective for curative involvement and may act as biomarker for medicine quarrel in patients of cancer. [8]

Serum amyloid A (SAA) protein

SAA protein is secreted by liver and its level in endometrial endometrioid cancer is high. So, to

check illness repetition and feedback to treatment, SAA protein may be a fresh biomarker for endometrial endometrioid cancer. [9]

Transcription factor POU6F1

POU6F1 expression on cell lines of epithelial ovarian cancer was established. Adenocarcinoma cell lines enhancement is decreased via POU6F1 siRNA. So it was concluded that the POU6F1; transcription factor might be a novel objective for the cure of ovarian tumor. [10]

PinX1 protein

Human interrelated protein X1 (PinX1); inhibitor of telomerase enzyme and expected to be a gene product that decrease the cancer growth. In a number of cancerous growths, overwhelm of pinX1 has been indicated but the exact state of appearance of pinX1 has not been found. So, concluded that pinX1 is an important molecular marker found on telomerase anticancer treatment for the ovarian cancer. [11]

Altered expression of ABC transporter gene

One of the causes of multiple drug resistance is ATP-binding cassette (ABC) transporters in a variety of cancers. The appearance of gene of transporters (ABCC1, ABCC2, and ABCB3) was considerably high in regular tumor wound in contrast to benign tumorous cells. So, decreased expression of ABC transporter gene may become a novel target for the ovarian cancer cells treatment. [12]

Inhibition of FEZ1 protein expression

Tumor inhibition takes place via FEZ1 gene and if its level becomes decreased then tumor develops very rapidly. But FEZ1 protein is related to ovarian cancer growth. So, it is suggested that if suppression of FEZ1 protein occur then it causes the recovery of ovarian cancer patient rapidly. [13]

Via endothelial progenitor cells (EPCs)

By means of endothelial progenitor cells (EPCs), when the sign that activate the immune system was released via blood, then it can change the tumor environment that resist the therapy and direct to a

beneficial outcome, which may give a new approach for target the malignancies of a number of varieties. [14]

Gene therapy based on interleukins

IL-12 gene delivery for ovarian cancer treatment

Insertion of human interleukin-12 plasmid/polyethyleneimine-cholesterol (phiIL-12/PPC) in ovarian cancer that are non responsive to treatment with chemicals was considered protected. During the route of phiIL-12/PPC management in PF model, intensity of IL-12 plasmid becomes noticeable in contrast to serum model. This information suggests the deliverance of IL-12 gene with a copied deliverance scheme become reasonable for treatment of ovarian malignancy. [15]

Endoplasmic strain by mda-7/IL-24

Melanoma differentiation associated gene-7/interleukin 24(mda-7/IL-24) causes the destruction of distorted cells and have no harmful effects on standard cells. So mda-7/IL-24 causes the destruction of endoplasmic reticulum that trigger manifold apoptotic passageway and become a cause of lessen endurance of ovarian cancer cell. [16]

Gene therapy based on angiogenesis inhibitors

AAV-K5 gene therapy of ovarian cancer

Plasminogen part i.e. Kringle 5 (K5) causes the inhibition of new blood vessel formation. Manifestation of Kringle 5 is obtained even when one I/V inoculation of adeno-associated virus (AAV-K5) was given to patient and it inhibited most of the malignant cell enhancement. Treatment with Kringle 5 gene has no effect on standard blood vessels but on the tumor vessels and causes fatality of ovarian cell. So, AAV-K5 therapy has significant role in hindrance of tumor growth. [17]

Enhanced secretion of Endostatin mediated by mesenchymal stem cells

Endostatin causes the inhibition of new blood vessel formation of cancer cells. A novel source of endostatin is Mesenchymal stem cells (MSCs) as they gathered at the place of tumor. SKOV3 cell were cultivated with MSC-EN cell to examine the effect of endostatin on tumor cell and death of tumorous cells was observed. So, it is concluded that slow down the propagation of SKOV3 cells was obtained by endostatin created via MSC-EN cells. [18]

INHIBITION OF OVARIAN CANCER BASED ON ICB-1 GENE

ICB-1 gene, the main task of which is to goal the estrogen hormone. Via shRNA plasmid its appearance is reduced in SK-OV-3 cells but in case of propagation, estrogen reaction of SK-OV-3 cells was obtained via reduction of ICB-1 gene. So, it is concluded that stoppage of propagation was obtained by ICB-1 gene that put forth the opposed actions on the estrogen retort of cells. [19]

ROLE OF MICRO-RNAs IN TREATMENT OF OVARIAN CANCER

A molecular class that manage gene appearance, microRNAs (miRNAs), takes part in ovarian growth. The majorities of deshaped microRNAs are decreased in tumor, and causes to decrease the cancer growth; others are prominent and may become the cancerous genes in this ailment. So, several microRNAs uttered in ovarian carcinoma and cause the tumor growth and show goal for treatment. [20]

GENE THERAPY BASED ON XIAP GENE (RNAI)

The propagation of ovarian carcinoma cell was obtained via repression of XIAP gene RNA interference (RNAi) and by the lessening of its mRNA and protein, cells become extra responsive to cisplatin. So these outcomes propose that XIAP is an oncogene and also that XIAP is a probable goal for drugs that use for the cancer treatment. [21]

HUMAN SPERM PROTEIN 17 (HSP17); A POTENT RISK FACTOR

In epithelial ovarian cancer cells, abnormal appearance of human sperm protein 17 (HSp17) was investigated and behavior of ovarian cell akin to relocation and resistance to treatment via chemicals by immunohistochemistry and immunocytochemistry were examined. Sympathy to chemicals of cancerous cells to carboplatin and cisplatin is decreased but enlarged the relocation by increased appearance of HSp17. So it may be concluded that HSp17 causes metastasis and confrontation of epithelial ovarian carcinoma to treatment with chemicals. [22]

GENE THERAPY BASED ON LYSOPHOSPHATIDIC ACID (LPA)

Unusual lysophosphatidic acid (LPA) making, receptor appearance, and indication are normally established in ovarian carcinomas telling that LPA involve in the physiology of the syndrome. LPPs enzymes that cause the deprivation and making of LPA and the improvement of receptor related-analogues unwrap a possible novel advancement in the cure of this lethal bug. Increased appearance of these enzymes goes back the normal condition and slows down the enlargement of the tumor cell. These findings propose that aiming of LPA may become actual adding to handling of this lethal ailment. [23]

ROLE OF TELOMERASE IN OVARIAN CANCER

Telomerase keeps the telomere length constant and prevent from cell death and considered as a goal for cancer treatment. In comparison with regular cells, its action is considerably prominent in malignant cells. To aim gene appearance in ovarian cells straightforwardly; human telomerase reverse transcriptase (hTERT; T) promoter was examined. GSK3 activate hTERT appearance in tumor cells and contribute to telomere span homeostasis. Xie et al. (2009) articulated E1A by the new VISA policy, in order to extend the appearance of this supporter gene appearance system into an appropriate remedial vector. We demonstrate that the T-VISA

scheme specially under attack E1A appearance to ovarian malignant cells at superior level or equivalent to the usually employed cytomegalovirus (CMV), a nonspecific promoter, though stayed almost calm down in regular cells. Deliverance of T-VISA-E1A nanoparticles, signifying an artistic task of T-VISA-E1A for ovarian tumor management underneath a gene treatment background. [24],[25]

ROLE OF H19 RNA IN OVARIAN CANCER TREATMENT

In human cancer cells (together with ovarian cancer), H19 RNA exist there at elevated stage than regular cells. By an H19 RNA probe, from ovarian cancer ascites fluid (OCAF) the appearance of H19 gene was experienced in cell via in-situ hybridization method (ISH). As demonstrated via ISH, in about 90% cases this H19 RNA was identifying with OCAF. DTA-H19 injection in tumor becomes a cause of 40% reservation of cancer enlargement. So, we built-up a novel treatment plans to goal the expression of diphtheria toxin gene under the direction of H19 dogmatic sequence in ovarian lumpy cells. [26]

ANTI-APOPTOTIC GENES ENHANCEMENT

When glucocorticoid administered to ovarian cancer patients, then expression of anti-tumor genes SGK1 and MKP1 has been increased. So, it is suggested that efficacy of treatment with chemicals is decreased by glucocorticoid administration because appearance of anti-apoptotic genes have been enhanced. [27]

ROLE OF ATP7B siRNA IN CANCER REMEDY

Under attack of small interfering RNA (siRNA) causes the silencing of genes ATP7A and ATP7B. siRNA, for *in vivo* experiments, integrated into the unbiased nanoliposome 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine (DOPC). Tumor growth in concoction with cisplatin had been largely decreased when ATP7B siRNA was integrated into DOPC. This lessening in cancer enlargement results in shortened propagation, condensed new blood vessel formation and amplified cancer cell death. This information gives a novel perceptive of cisplatin confrontation in tumor cells and may give the

information about curative turnaround of remedy conflict. [28]

ROLE OF ID1 IN OVARIAN CANCER TREATMENT

In ovarian cancer, ID1 (inhibitor of differentiation or DNA binding protein 1) level is found to be high and its greater intensity indicates the malignancy in cancerous cells. So, ID1 is a probable objective for ovarian tumor healing. By activating transcription factor 3 (ATF3), Apigenin, an ordinary nutritional flavonoid, concealed the appearance of ID1. Our consequences may clarify a novel scheme indicating the preventive outcome of apigenin on malignant cells. [29]

ESTROGEN RECEPTOR ROLE IN EPITHELIAL OVARIAN CANCER

In quietness of estrogen receptor (ER) appearance, function of epigenetic have recommended when ruling of the estrogen receptor (ER) had been considered. With bisulfite sequencing, ERbeta supporter methylation was studied. Hypomethylation of the ERbeta promoter in SKOV3 compare to HEY cell was found and also the methylation of Cell type-specific ERbeta supporter was created. 5-aza-2'-deoxycytidine (AzaC) and trichostatin (TSA) cause considerable cancer development reticence and modification in appearance of many genes. So, it is suggested that AzaC and TSA can reduce ovarian tumor cell enlargement and methylation of ERbeta advertiser takes place in ovarian tumor cells. [30]

PPM1D CURATIVE TARGET FOR OVARIAN CELL CARCINOMAS

In order to know the remedial objective in ovarian carcinomas, the outcome of reticence of PPM1D were judged by a tiny inhibitor of molecule (CCT007093) and by production of little hairpin RNA. PPM1D appearance and phosphatase action are very essential for the endurance of ovarian apparent cell cancerous cell outlines via 17q23.2 intensification as shown by the PPM1D silencing. PPM1D gene enlargement in principal ovarian

apparent cell is related with PPM1D expression levels. Our information gives sturdy incidental proof that PPM1D is a probable curative target for ovarian apparent cell carcinomas. [31]

TUMOR GROWTH SUPPRESSION VIA INACTIVATION OF ERYTHROPOIETIN RECEPTOR APPEARANCE

In cancerous patients, recombinant human erythropoietin (rHuEpo) exercise might be related with diminished endurance. Elevated intensity of EpoR appearance demonstrated by A2780 ovarian cancerous cells but be deficient in appearance of Epo mRNA and organically energetic Epo protein underneath mutually normal and the situation in which oxygen level is decreased. So it is concluded that, in the dearth of Epo, EpoR may be energetic in a number of tumor cells and give the primary confirmation for a probable task of an Epo-sovereign, EpoR-arbitrated alleyway in the enlargement of a number of individual tumor. [32]

YIN YANG 1 GENE ROLE IN CANCER TREATMENT

YIN YANG 1 (YY1) gene appearance is absolutely connected through ovarian tumor endurance. When the patients are treated by paclitaxel then the chances of patient's endurance is increased due to elevated YY1/E2F3 action. YY1 reduction in ovarian tumor cell outline enhances opposition to taxanes as therapeutic efficacy of cisplatin remains constant, but also causes reticence of enlargement, movement, and propagation. So it can be concluded that E2F3, microtubule-associated genes are increased and taxane consideration in cancer is improved by elevated YY1/E2F action and these might be arbitrate by variation of assumed objective genes by way of microtubule role. [33]

GRP94 siRNA HELPFUL IN GENE THERAPY OF OVARIAN CANCER

HO-8910PM cells show the lowly compassion to Adriamycin by the maximum basal level of glucose regulated protein 94 (GRP94). By definite siRNA in HO-8910PM cells, the repression of GRP94 appearance was achieved. By exact siRNA transfection, In HO-8910PM cells, by decreasing the GRP94 gene,

compassion to Adriamycin were amplified. So, it is suggested that in cancer-precise gene treatment in ovarian malignancy, GRP94 siRNA perhaps helpful. [34]

OVARIAN GROWTH SUPPRESSION VIA TAT-ELP

Massodi et al. (2009) established that peptide Tat, combined by elastin-like polypeptide (ELP) causes the reservation of linkage, dispersal, attack and relocation of SKOV-3 ovarian malignant cells in cell civilization. Actually Tat-ELP have very less possibility of metastases causes 80% decrease in the cancer weight as shown in an investigational ovarian cancer metastasis mold in vivo. These findings recommend a narrative function of Tat-ELP as a beneficial interference in tumor metastasis. [35]

Conclusion

Many workers are in the search of gene therapy for ovarian cancer and it may prove to be better as compared to chemotherapy due its comparable therapeutic effects.

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