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Mechanisms Resistance Cancer Cells to Cytotoxic Anticancer Drugs and Relapsed Cancer disease after Chemotherapy

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Abstract

There were shown shortcoming of intensive chemotherapeutic methods with great dosage cytotoxic drugs causing as destruction some cancer cells as well as suppression hormonal and immune defensive mechanisms. Considering mechanisms of oncogenesis and appearance resistance cancer cells to some cytotoxic drugs as well as relapsed cancer disease after temporary ceased chemotherapy, there were described mechanisms resistance to cytotoxic drugs causing by immune mechanisms and recovered of suppressed hormonal system of an organism as well as mechanism of relapsed cancer disease. Also there were substantiated the mechanisms resistance to cytotoxic drugs and mechanism relapse cancer disease via describing genetic mechanisms of cancer cellular cycle in processes of resistance to cytotoxic drugs and relapse cancer disease from the point of view of thermodynamics. Besides there were discussed investigations of resistance to cytotoxic drugs and relapse cancer disease causing by the different authors.

Kaywords: Relapse cancer disease, Resistance to cytotoxic drugs, Meiosis-Mitosis phase of cancer cellular cycle, oncologic viruses [v-oncogenes], hormones, T memory cells, T helper cells, T killer cells, B cells, Basic Internal Energy (E_{basic}), Stem cells.

Introduction

The prevalanse etiologic factors over organism's defensive immune and hormonal systems stimulates driving mechanisms of transmutating normal cells into cancer cells which lead to development of cancer cells. Oncologic viruses affect cells' nuclei of weak place of extracellular tissue which is supplied with lack of Basic Internal Energy (E_{bas}) causing by lack of hormonal support. Lack of cellular walls' hormonal support results in disbalance cellular chemical potential ($\mu_{inter.cell}$) & extracelluar chemical potential ($\mu_{outer.cell}$). Thus oncologic viruses (v-oncogenes) affect deep level of stem cells maybe Unipotent stem cells or even Oligopotent stem cells due to lack of Basic Internal Energy (E_{bas}). The modern chemotherapy with great dosage cytotoxic drugs leads to complete destruction some oncologic viruses and some suppression defensive mechanisms of immune and hormonal systems. Just suppressed defensive mechanisms of immune and hormonal systems of an organism lead to expression some survived oncologic viruses due to pause of intersive chemotherapy which use suppressed defensive immune and hormonal factors opposed cytotoxic drugs of modern chemotherapeutic methods cancer treatment causing with great dosage cytotoxic drugs resulting in resistance cancer cells to cytotoxic anticancer drugs and relapsed cancer disease.

Mechanisms of resistance to cytotoxic drugs and relapse cancer disease after intensive modern methods cancer chemotherapy

The development of cellular cycle demand energy for the supplemental anabolic biosynthetic endergonic processes which energy is received from Basic Internal Energy (Ebasic) of an organism through Basic stem cells (neurons) → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → Unipotent stem cells → type healthy cells and Basic stem cells (neurons) → Totipotent stem cells → Pluripotent stem cells → Multipotent stem cells → Oligopotent stem cells → either Unipotent stem cells in norm or Unipotent cancer stem cells in cancer pathology. Thus the induced inner cells and outer cells chemical potentials (μ) via transition chemical potentials (μ) through relative G1 → S → G2 phases cellular cycle are the mechanism which realize driving mechanism cellular cycle in norm and cancer pathology reflecting positive fluctuations entropy ($+\Delta_x\beta$) and negative fluctuation entropy ($-\Delta_x\beta$) advancing cellular cycle through G0/G1/S/G2/M phases according Glansdorff-Prigogine theory (Figure 1) [1,2]. Hence Stationary State of healthy cells, being affected by viral oncogenes, are arisen excessive anabolic endergonic processes showing negative fluctuations entropy ($d_x\beta < 0$) which transits S phase cellular cycle of cancer cells thermodynamic system into G2 phase cellular cycle and then similar transit G2 phase into cancer Meiosis-Mitosis phase of Quasi-stationary cancer pathologic State according to Glansdorff & Prigogine theory (Figure 1). This thermodynamic mechanism exerts operation Mitosis-Meiosis cancer cellular cycle because of affected both nuclear DNA and mitochondria of an organosm's cells. Modern methods cancer therapy use following targets: cancer tumors, cancer cells, cancer cells' nucleus and its DNA, cancer cells' mitochondria, cancer cells' organelle as well as links between them.

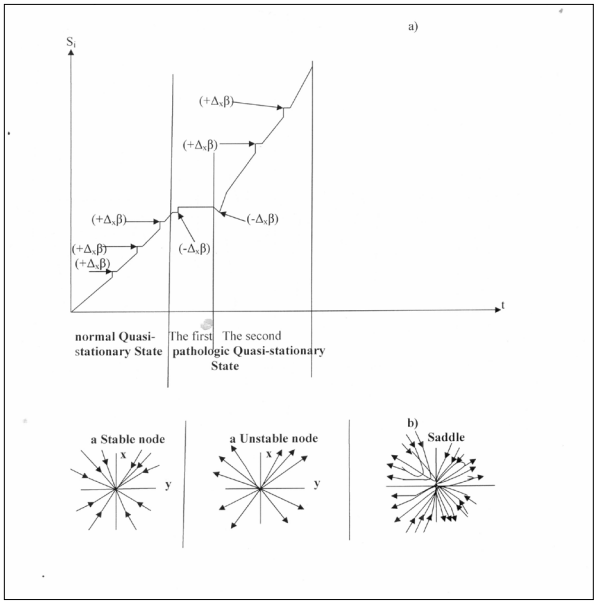

Figure 1: Change fluctuations of an entropy from normal stationary state into pathologic Quasistationary State

Fedier A. et al. studied DNA minor groove binded by Brostallicin (PNU-166196) causing cytotoxic effect on cancer tumor activity with its cancer cells and also retaining sensitivity to Brostallisin in deficient of DNA mismatch repair proteins functionas, i.e. sensitivity to Brostallisin does not depend on DNA MMR function [3]. However the intensive cellular cycles of immune cells and hormonal cells need DNA repairing especially. Just phagocytosis requires permanent new immune cells forming by reticuloendothelial system (RES) and by marrow, as wellas producing hormones by hormonal glands are required both by an organism cells' cellular cycles and by cancer cells' accelerating intensive cellular cycle. Therefore DNA minor grooves of immune cells and DNA minor grooves of hormonal cells are also binded by Brostallicin (PNU-166196) although normal cells in less rate than cancer cells. However violation immune and hormonal function of an organism causes common disbalance anabolic endergonic processes & catabolic anaerobic exergonic processes & catabolic aerobic exergonic processes of Quasi-stationary pathologic State of an organism supplementally to accelerating cancer cellular cycle. Besides oncogenesis can leads as to resistance cancer cells to cytotoxic anticancer drugs as well as to relapsed cancer disease after intensive cytotoxic therapy due to following mechanisms. Just resistance cancer cells to cytotoxic anticancer drugs and relapsed cancer disease are occurred after some times of intensive chemotherapeutic treatment with cytotoxic drugs which affect nuclear DNA (nDNA) suppressing as G1/S/G2 phases cancer cellular cycle as well as Meiosis-Mitosis phase cancer cellular cycle. Suppretion Meiosis-Mitosis phase cancer cellular cycle touch on as oncologic viral prokaryotic genome as well as human eukaryotic genome. It is occurred resistance between antiviral force of drugs and oncologic viral force for viral survival in which transition Meiosis-Mitosis into Mitosis-Meiosis reflects prevalence antiviral force of drugs. But retaining Meiosis-Mitosis reflects prevalence oncologic viral force for viral survival in which viruses [v-oncogenes] use rest hormonal mechanisms of hormonal glands (not damaged by cytotoxic drugs) for supporting cancer cells development via accelerating cellular cycle [2, 4]. Just retaining Meiosis-Mitosis cancer cellular cycle of survived oncologic viruses [v-oncogenes] retains accelerating cancer cellular cycle which is supported by rest hormonal mechanisms of some hormones activity after some time of intensive cytotoxic drugs treatment. Thus it gives possibility some survived oncologic viruses [v-oncogenes] to create relapsed cancer disease after some time of intensive cytotoxic therapy. Besides rest some hormones activity of hormonal glands and immune T memory cells, T helper cells, T killer cells with B cells are restored after some time of intensive cytotoxic drugs treatment in which hormones activity restore immune T memory cells, T helper cells, T killer cells. The immune T memory cells learn molecules of cytotoxic drugs into hormonal gland's cells injured by these cytotoxic drugs. Then T memory cells transmit these data to T helper cells and further to T killer cells. The T killer cells destruct these cytotoxic drugs causing resistance to these anticancer drugs (Figure 2). As concerning using some hormone activity by survived rest oncologic viruses, it must be explained the following example: In breast cancer cells after intensive cytotoxic therapy it is occurred either resistance to cytotoxic drugs or relapse cancer disease because cytotoxic drugs suppress cancer Meiosis-Mitosis cellular cycle and simultaneously suppress as immune T memory cells, T helper cells, T killer cells as well as activity female Estrogens [estrone, estradiol, estriol] and Progesterone hormones. After some time from intesive chemotherapy, it is begun expression as restored immune T memory cells, T helper cells, T killer cells as well as activity female estrogens [estrone, estradiol, estriol] and Progesterone hormones in which restored activity of estrogens can prevail over restored activity of progesterone causing shift balance estrogens & progesterons into expression estrogens. Therefore estrogens [estrone, estradiol, estriol] either restore activity of suppressed cancer cells after some time of chemotherapy inducing relapse cancer disease or exert expression as restored immune T cells in which T memory cells learn molecule of cytotoxic drugs into hormonal gland's cells injured by these drugs. Then T memory cells transmit the data of molecules cytotoxic drugs to T helper cells and further to T killer cells. The T killer cells destruct these cytotoxic drugs causing resistance to these anticancer drugs. Thus excessive estrogens [estrone, estradiol, estriol] operate how carcinogens. The balance sexual hormons estrogens & progesterons induce normal development female organism from pubertal age till climacteric age where progesteron is expressed. On the other hand, often molecules of some cytotoxic drugs don't leave data of theirs genomes in substances of hormonal glands' injured cells, and T memory cells don't learn their molecules. Therefore these cytotoxic drugs are not subjected to destruction of their molecules by T killer cells. Thus there are not resistance to anticancer activity of these cytotoxic drugs.

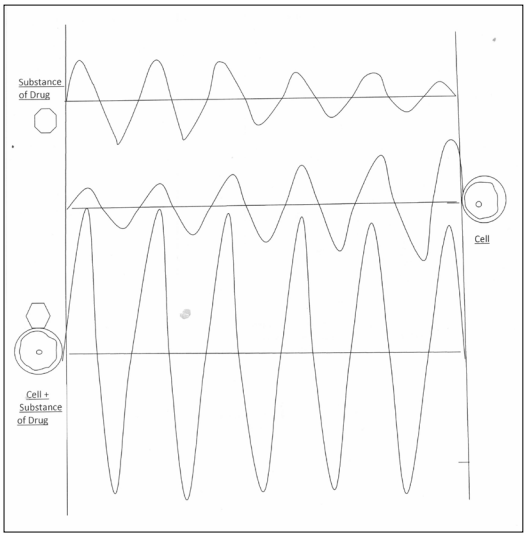

Figure 2: T cell Disordered resonance waves on strange drug's substances causing resistance to cytotoxic drug

Discussion mechanisms of resistance to cytotoxic drugs and relapse cancer disease after intensive modern methods cancer chemotherapy

Meyers M. et al. studied mechanism cytotoxic action Fluoropyramidine causing damage processes biosynthesis proteins via translations and transcription DNA processes requiring mechanism of DNA reparation via operation DNA mismatch repair proteins function. Author did not find differences sensitivity to Fluoropyramidine between MMR-deficient cancer cells and MMR-proficient cancer cells [5].

However Fluoropyramidine causes also violation processes biosynthesis immune antibodies by immune system and hormones by hormonal glands. Thus damage biosynthesis of proteins causing by Fluoropyramidine violates immune and hormonal cells' functions although in less rate than cancer cells. Just violation immune and hormonal function of an organism causes violation common balance anabolic endergonic processes & catabolic anaerobic exergonic processes & catabolic aerobic exergonic processes of Quasi-stationary pathologic State of an organism. The violation common balance anabolic endergonic processes & catabolic anaerobic exergonic processes & catabolic aerobic exergonic processes can lead as to expression resistance cancer cells to cytotoxic activity of Fluoropyramidine as well as to relapsed cancer disease after intensive cytotoxic therapy because chemotherapeutic treatment with Fluoropyramidine affect nuclear DNA (nDNA) suppressing Meiosis-Mitosis phase cancer cellular cycle which touch on as oncologic viral [v-oncogenes] prokaryotic genome as well as human eukaryotic genome. It is occurred resistance between antiviral force of Fluoropyramidine and oncologic viral force [v-oncogenes] for survival in which transition Meiosis-Mitosis into Mitosis-Meiosis reflects prevalence antiviral force of Fluoropyramidine. But retaining Meiosis-Mitosis reflects prevalence viral force for viral survival for which viruses [v-oncogenes] use rest hormonal mechanisms (not damaged by Fluoropyramidine) for supporting cancer cells development via accelerating cellular cycle [2, 4]. Just retaining Meiosis-Mitosis cancer cellular cycle of survived oncologic viruses [v-oncogenes] has also accelerating cancer cellular cycle which is supported by rest hormonal mechanisms of some hormones activity after some time of intensive cytotoxic Fluoropyramidine treatment. Thus it gives possibility survived some oncologic viruses [v-oncogenes] to create relapsed cancer disease after some time of intensive cytotoxic therapy. Besides rest hormonal glands of some hormones activity and immune T memory cells, T helper cells, T killer cells with B cells are restored after some time of intensive cytotoxic activity of Fluoropyramidine treatment in which hormones restore activity of immune T memory cells, T helper cells, T killer cells. The immune T memory cells learn molecule of Fluoropyramidine in hormonal gland's cells injured by Fluoropyramidine. Then T memory cells transmit the data of molecule Fluoropyramidine to T helper cells and further to T killer cells. Hence T killer cells destruct Fluoropyramidine causing resistance to the anticancer activity of Fluoropyramidine. However molecules of some cytotoxic drugs don't leave data of theirs genomes in substances of injured cells of hormonal glands, and T memory cells don't learn their molecules. Therefore these cytotoxic drugs are not subjected to destruction of their molecules by T killer cells. Thus there are not resistance to anticancer activity of these cytotoxic drugs.

Sergent C. et al. studied mechanism of cytotoxic actions cisplatin and oxaliplatin in vitro, and their researches on colon cancer cells are resulted in high-level resistance of human colon cancer cells to high doses of cisplatin which does not been related to acquired defects in the DNA repaired by MMR proteins [6]. Thus cytotoxic property of cisplatin acts on biosynthesis proteins via damaging translations and transcription DNA processes causing reparation by DNA mismatch repair proteins function, but cytotoxic property of cisplatin does not act on DNA reproduction for cellular proliferation. Just all necessary proteins for cells proliferations were used for experiment in vitro. Therefore survival of cancer cells in condition obtained high doses of cisplatin or oxaliplatin does not relate to acquired defects in the DNA repaired by MMR proteins corresponding to the outcomes of Sergent C. et al.

However cytotoxic property of cisplatin causes also violation processes biosynthesis immune antibodies by immune system and hormones by hormonal glands in vitro especially. However damage biosynthesis of proteins causing by cisplatin violates immune and hormonal cells' functions although in less rate than cancer cells in vivo. Just violation immune and hormonal function of an organism causes violation common balance anabolic endergonic processes & catabolic anaerobic exergonic processes & catabolic aerobic exergonic processes of Quasi-stationary pathologic State of an organism that can lead to resistance cancer cells to cytotoxic anticancer cisplatin after intensive cytotoxic therapy because chemotherapeutic treatment with cisplatin and oxaliplatin affect nuclear DNA (nDNA) suppressing as G1/S/G2 phases cancer cellular cycle as well as Meiosis-Mitosis phase cancer cellular cycle which touch on as oncologic viral [v-oncogenes] prokaryotic genome as well as human eukaryotic genome. It is occurred resistance between antiviral force of cisplatin and oncologic viral force [v-oncogene] for survival in which transition Meiosis-Mitosis into Mitosis-Meiosis reflects prevalence antiviral force of cisplatin. But retaining Meiosis-Mitosis reflects prevalence viral force for viral survival in which viruses [v-oncogenes] use rest hormonal mechanisms (not damaged by cisplatin) for supporting cancer cells development via accelerating cellular cycle [2, 4]. Just retaining Meiosis-Mitosis cancer cellular cycle of survived oncologic viruses [v-oncogenes] use also accelerating cancer cellular cycle which is supported by rest hormonal mechanisms of some hormones activity after some time of intensive cytotoxic cisplatin treatment. Thus rest hormonal glands of some hormones activity and immune T memory cells, T helper cells, T killer cells with B cells are restored after some time of intensive cytotoxic cisplatin treatment in which hormones restore activity of immune T memory cells, T helper cells, T killer cells. The immune T memory cells learn molecule of cisplatin in hormonal gland's cells injured by cisplatin. Then T memory cells transmit these data of cisplatin molecule to T helper cells and further to T killer cells. The T killer cells destruct molecule of cisplatin causing resistance to the anticancer activity of cisplatin. Besides it gives possibility some survived oncologic viruses [v-oncogenes] to create relapsed cancer disease after some time of intensive cytotoxic therapy. However it can be situation that molecules of some cytotoxic drugs don't leave data of theirs genomes in substances of injured cells of hormonal glands, and T memory cells don't learn their molecules. Therefore these cytotoxic drugs are not subjected to destruction of their molecules by T killer cells. Thus there are not resistance to anticancer activity of these cytotoxic drugs. Just this situation can be arisen in experiment in vitro.

Stubbert LJ. et al. studied mechanism of resistance to cytotoxic action cisplatin in cancer cells [7]. Their researches on several prostate cancer cells and colorectal carcinoma cells are resulted in following data. Cisplatin resistance is multi-factorial process but can be associated with DNA repair capacity either mutations

with p53 or loss DNA mismatch repair capacity.

However these processes don't lead to resistance to cytotoxic action cisplatin in cancer cells without operations immune defensive mechanisms. Indeed cytotoxic actions of cisplatin on biosynthesis proteins results in decreased transcription-coupled nucleotide leading to damaging translations in DNA biosynthesis proteins processes as in cancer cells as well as in an organism's immune and hormonal cells. Thus citotoxic property cisplatin causes violation processes biosynthesis immune antibodies by immune system and hormones by hormonal glands. But damage biosynthesis of proteins causing by cisplatin violates immune and hormonal cells' functions although in less rate than cancer cells. Just violation immune and hormonal function of an organism causes violation common balance anabolic endergonic processes & catabolic anaerobic exergonic processes & catabolic aerobic exergonic processes of Quasi-stationary pathologic State of an organism that can lead to resistance immune system to cytotoxic anticancer cisplatin after intensive cytotoxic therapy because chemotherapeutic treatment with cytotoxic activity of cisplatin violate nuclear DNA (nDNA) suppressing as G1/S/G2 phases cancer cellular cycle as well as Meiosis-Mitosis phase cancer cellular cycle which touch on as oncologic viral [v-oncogenes] prokaryotic genome as well as human eukaryotic genome. It is occurred resistance between antiviral force of cisplatin and oncologic viral force [v-oncogenes] for survival in which transition Meiosis-Mitosis into Mitosis-Meiosis reflects prevalence antiviral force of cisplatin. But retaining Meiosis-Mitosis reflects prevalence viral force for viral survival for which viruses [v-oncogenes] use rest hormonal mechanisms (not damaged by cisplatin) for supporting cancer cells development via accelerating cellular cycle [2, 4]. Just retaining Meiosis-Mitosis cancer cellular cycle of survived oncologic viruses [v-oncogenes] use also accelerating cancer cellular cycle which is supported by rest hormonal mechanisms of some hormones activity after some time of intensive cytotoxic cisplatin treatment. Thus rest hormonal glands of some hormones activity and immune T memory cells, T helper cells, T killer cells with B cells are restored too after some time of intensive cytotoxic activity of cisplatin treatment in which hormones restore activity of immune T memory cells, T helper cells, T killer cells. The immune T memory cells learn molecule of cislatin into hormonal gland's cells injured by cisplatin. Then T memory cells transmit the data of cisplatin molecule to T helper cells and further to T killer cells. The T killer cells destruct cisplatin causing resistance to cisplatin. Besides it gives possibility some survived oncologic viruses [v-oncogenes] to create relapsed cancer disease after some time of intensive cytotoxic therapy. However it can be situation that molecules of some cytotocsic drugs don't leave data of theirs genomes in substances of injured cells of hormonal glands, and T memory cells don't learn their molecules. Therefore these cytotoxic drugs are not subjected to destruction of their molecules by T killer cells. Thus there are not resistance to anticancer activity of these cytotoxic drugs. So it can be explained multi-factorial processes of either cisplatin rasistance or not resistance to cisplatin in different researches.

Lin X. and Howell S.B. examined influences loss of p53 or DNA mismatch repair proteins (MMR) function on resistance to cisplatin, i.e. they examined mechanism resistance to cisplatin in loss of p53 or DNA mismatch repair (MMR) function [8]. Just DNA mismatch repair proteins and p53 function are major determinants of the rate cisplatin resistance concerning to the outcomes of their researches. Also Lin X. and Howell S.B. proclaim "As opposed to factors that control sensitivity to the cytotoxic effect of cisplatin, little is known about the factors that determine the reaction which resistance develops". Thus Lin X. and Howell S.B. made conclusion that separate from effects on sensitivity to the cytotoxic effect of cisplatin, loss of MMR, especially when it combined with loss of p53, results in rapid evolution of cisplatin resistance during sequential rounds of drug exposure that is likely mediated by enhanced mutagenic translation synthesis. The DNA damage response activated by cisplatin is accompanied by a p53- and MMR-dependent increase in homologous recombination even between adduct of free sequences. Further Lin X. et al. studied P53 modulates the effect of loss of DNA mismatch repair on the sensitivity of human colon cancer cells to the cytotoxic and mutagenic effects of cisplatin [9]. Their experiments are shown that disruption of p53 in MMR-deficient HCT116 cells resulted in substantial levels of resistance to some agents (paclitaxel, 1.9-fold; gemcitabine, 2.7-fold; 6-thioguanine, 3.3-fold; and etoposide, 4.4-fold) but low sensitization to other agents (topotecan, 2.5-fold; and DDP, 3.3-fold). Loss of MMR or p53 alone had only minor effect on sensitivity to the mutagenic effect of DDP as measured by the appearance of variants resistant to 6-thioguanine, etoposide, topotecan, gemcitabine, and paclitaxel in the population 10 days later (1.0-2.4-fold), whereas loss of both p53 and MMR had a more profound effect (1.7-6.5-fold). Loss of both p53 and MMR increased the basal frequency insertion/deletion mutations detected by a shuttle vector-based assay to a greater extent than loss of either alone. The Lin X. et al. note that these results indicate that p53 and MMR can cooperate to control sensitivity to the cytotoxic effect of DDP and to limit its mutagenic potential in the colon cancer cells.

However Lin X. et al. researches don't determine mechanism of resistance to cisplatin and other cytotoxic drugs, but they determine results of their negative actions which happened simultaneously with resistance to cytotoxic action of these drugs. Also researches LinX et all expose both mutual interaction between relative mechanisms p53 cancer suppressor binding chromosome 17, DNA Mismatch Repair Protein (MMR) acting as in interphase S / G2 as well as on chromosome 3 in Mitosis (M) phase and resistance to cytotoxic drugs by cancer cells, i.e. not separating either interactions on driving mechanism cellular cycle which advances due to interactions as between nuclear center anabolic processes and mitochondrial center catabolic processes of defensive mechanisms inner cells or resistance to cisplatin influences on cancer cells by defensive mechanisms of immune mechanism of an organism in outer cells medium. These interactions are realized by alternations inflow and outflow substances and energy forming prevalence intracellular chemical potential ($\mu_{inner\ cell}$) or extracellular chemical potential ($\mu o_{uter\ cell}$) [$\mu_{inner\ cell} > \leftrightarrow < \mu_{outer\ cell}$] corresponding to Theorell equation which realize driving mechanism cancer cycle and cancer development reflecting positive fluctuations ($+\Delta_x\beta$) and negative fluctuation entropy ($-\Delta_x\beta$) advancing cellular cycle through G0/G1/S/G2/M phases according Glansdorff-Prigogine theory (1, 2) (Figure 1.). Therefore influences both p53 and MMR [loss or activity, deficient or proficient] are mechanisms of cellular cycle in able-bodied cells and cancer cells. But resistance to diferent cytotoxic drugs depend as on cancer cells reaction against cytotoxic activity drug via rearranged cellular cycle for cancer cells survival (see above) as well as on immune cells reactions on substances of cytotoxic drug corresponding to Schreodinger method of the molecular orbitals – a linear combination of atomic orbitals (MO LCAO). Just target of chemotherapeutic treatment with cisplatin and other cytotoxic drugs affect nuclear DNA (nDNA) suppressing as G1/S/G2 phases an organism's cells' cellular cycle as well as Meiosis-Mitosis phase cancer cellular cycle which touch on as oncologic viral [v-oncogenes]

prokaryotic genome as well as human eukaryotic genome. It is occurred resistance between antiviral force of cisplatin or of other cytotooxic drugs and oncologic viral [v-oncogene] force for survival in which transition Meiosis-Mitosis into Mitosis-Meiosis reflects prevalence antiviral force of cisplatin. But retaining Meiosis-Mitosis reflects prevalence viral force for viral survival for which viruses [v-oncogenes] use rest hormonal mechanisms (not damaged by cisplatin) for supporting cancer cells development via accelerating cellular cycle [2, 4]. Just retaining Meiosis-Mitosis cancer cellular cycle of survived oncologic viruses [v-oncogenes] uses also accelerating cancer cellular cycle which is supported by rest hormonal mechanisms of some hormones activity after some time of intensive cytotoxic drugs treatment. Thus rest hormonal glands of some hormones activity and immune T memory cells, T helper cells, T killer cells with B cells are restored after some time of intensive cytotoxic drugs treatment in which hormones restore activity of immune T memory cells, T helper cells, T killer cells. The immune T memory cells learn molecule of cisplatin into hormonal gland's cells injured by cisplatin. Then T memory cells transmit the data of cisplatin molecule to T helper cells and further to T killer cells. The T killer cells destruct the molecule of cisplatin causing resistance to the anticancer activity of cisplatin. Besides it gives possibility some survived oncologic viruses [v-oncogenes] to create relapsed cancer disease after some time of intensive cytotoxic therapy. However molecules of some cytotoxic drugs don't leave data of theirs genomes in substances of injured cells of hormonal glands, and T memory cells don't learn their molecules. Therefore these cytotoxic drugs are not subjected to destruction of their molecules by T killer cells. Thus there are not resistance to anticancer activity of these cytotoxic drugs.

Nehmé A. et al. studied inducing of JNK and c-Abl signalling by cisplatin and oxaliplatin in mismatch repair-proficient and -deficient cells causing resistance to theses cytotoxic drugs [10]. Their studies have shown that loss of DNA mismatchrepair results in resistance to cisplatin but not to oxaliplatin, supposing that the mismatch repair proteins serve as a detector for cisplatin but not oxaliplatin adduct. The identifying the transduction pathways with the detector communicates, they investigated the effect of loss DNA mismatch repair on activation of known damage-responsive pathways, and recently reported that cisplatin differentially activates c-Jun NH2-terminal kinase (JNK) and c-Abl in repair-proficient vs.-deficient cells.

Nehme A. et al. don't determine chemotherapeutic targets of cancer cells which were chosen for cytotoxic treatment by cisplatin and oxaliplatin [10]. Just target of chemotherapeutic treatment with cisplatin and oxaliplatin affect nuclear DNA (nDNA) suppressing as G1/S/G2 phases cancer cellular cycle as well as Meiosis-Mitosis phase cancer cellular cycle which touch on as oncologic viral [v-oncogene] prokaryotic genome as well as human eukaryotic genome. It is occurred resistance between antiviral force of cisplatin or oxaliplatin and oncologic viral [v-oncogene] force for survival in which transition Meiosis-Mitosis into Mitosis-Meiosis reflects prevalence antiviral force of cisplatin. But retaining Meiosis-Mitosis reflects prevalence viral force for viral survival in which viruses [v-oncogenes] use rest hormonal mechanisms (not damaged by cisplatin) for supporting cancer cells development via accelerating cellular cycle (2, 4). Just retaining Meiosis-Mitosis cancer cellular cycle of survived oncologic viruses [v-oncogenes] uses accelerating cancer cellular cycle which is supported by rest hormonal mechanisms of some hormones activity after some time from intensive cytotoxic drugs treatment. Thus rest hormonal glands of some hormones activity and immune T memory cells, T helper cells with B cells are restored after some time from intensive cytotoxic drugs treatment in which hormones restore activity of immune T memory cells, T helper cells, T killer cells. The immune T memory cells learn molecule of cisplatin in hormonal gland's cells injured by cisplatin. Then T memory cells transmit the data of cisplatin molecule to T helper cells and further to T killer cells. The T killer cells destruct the molecule of cisplatin causing resistance to the anticancer activity of cisplatin. Besides it gives possibility some survived oncologic viruses [v-oncogenes] to create relapsed cancer disease after some time of intensive cytotoxic therapy. However some molecules of cytotoxic drugs don't leave data of theirs genomes in substances of injured cells of hormonal glands, and T memory cells don't learn their molecules. Therefore these cytotoxic drugs are not subjected to destruction of their molecules by T killer cells. Thus there are not resistance to anticancer activity of these cytotoxic drugs. Only response of an organism's sensibilized immune system of T cells via sequence T memory cells → T helper cells → T killer cells through relative resonance waves of their cellular capacitors can results in resistance to cisplatin influences, but not resistance to oxaliplatin. Just resistance to diferent cytotoxic drugs depend on resonance waves of immune cells' capacitors reactions on substances cytotoxic drug corresponding to Schreodinger method of the molecular orbitals – a linear combination of atomic orbitals (MO LCAO).

Fink D, et al. studied role of DNA mismatch repair in platinum drug resistance [11]. Loss of DNA mismatch repair occurs in many types of tumors. The effect of the loss of DNA mismatch repair activity on sensitivity to cisplatin and a panel of analogues drugs were tested using two pairs of the DNA mismatch repair proteins in cell lines proficient or deficient of this function. HCT116+ch2, a human colon cancer cell line deficient in hMLH1, was 2.1-fold resistant to cisplatin and 1.3-fold resistant to carboplatin when compared to a subline complemented with chromosome 3 expressing a wild-type copy of hMLH1. Likewise, the human endometrial cancer cell line HEC59, which is deficient in hMSH2, was 1.8-fold resistant to cisplatin and 1.5-fold resistant to carboplatin when compared to a subline complemented with chromosome 2 with a wild-type hMSH2. In contrast to cisplatin and carboplatin, which form the same types of adducts in DNA, there was no difference in sensitivity between the DNA mismatch repair-proficient and -deficient cell lines for oxaliplatin, tetraplatin, transplatin, JM335, or JM216. The formation of protein-DNA complexes that contained hMSH2 and hMLH1 was documented by mobility shift assay when nuclear extracts were incubated with DNA platinated with cisplatin but not with oxaliplatin. These results demonstrate a correlation between failure of the DNA mismatch repair proteins to recognize the platinum adduct and low-level resistance, suggesting a role the DNA mismatch repair system in generating signals that contribute to the generation of apoptotic activity. They also identify the use of drugs whose adducts are not recognized as a strategy for circumventing resistance due to loss of DNA mismatch repair.

Fink D. et al. don't determine chemotherapeutic targets of cancer cells which were chosen for cytotoxic treatment by platinum drugs resistance [11]. Just target of chemotherapeutic treatment with cisplatin and other platinum drugs affect nuclear DNA (nDNA) suppressing as G1/S/G2 phases cancer cellular cycle as well as Meiosis-Mitosis phase cancer cellular cycle which touch on as oncologic viral [v-oncogene] prokaryotic genome as well as human eukaryotic genome. It is occurred resistance between antiviral force of cisplatin or other platinum drugs and oncologic viral [v-oncogene] force for survival in which transition Meiosis-

Mitosis into Mitosis-Meiosis reflects prevalence antiviral force of cisplatin or other platinum drugs. But retaining Meiosis-Mitosis reflects prevalence viral force for viral survival for which viruses [v-oncogenes] use rest hormonal mechanisms (not damaged by cisplatin or other platinum drugs) for supporting cancer cells development via accelerating cellular cycle (2, 4). Just retaining Meiosis-Mitosis cancer cellular cycle of survived oncologic viruses [v-oncogenes] use also accelerating cancer cellular cycle which is supported by rest hormonal mechanisms of some hormones activity after some time from intensive cytotoxic of some platinum drugs treatment. Thus rest hormonal glands of some hormones activity and immune T memory cells, T helper cells, T killer cells with B cells are restored after some time of intensive cytotoxic platinum drugs treatment in which hormones restore activity of immune T memory cells, T helper cells, T killer cells. The immune T memory cells learn molecule of cisplatin or other platinum drugs in hormonal gland's cells injured by cisplatin or other platinum drugs. Then T memory cells transmit the data of cisplatin or other platinum drugs molecules to T helper cells and further to T killer cells. The T killer cells destruct the molecule of cisplatin or other platinum drugs causing resistance to the anticancer activity of cisplatin or other platinum drugs. Besides it gives possibility some survived oncologic viruses [v-oncogenes] to create relapsed cancer disease after some time from intensive cytotoxic therapy. However some molecules of platinum drugs don't leave data of theirs genomes in substances of injured cells of hormonal glands, and T memory cells don't learn their molecules. Therefore these platinum drugs are not subjected to destruction of their molecules by T killer cells. Thus there are not resistance to anticancer activity of these cytotoxic palatinum drugs. Just resistance to diferent cytotoxic drugs depend on resonance waves of immune cells' capacitors reactions on substances cytotoxic drug corresponding to Schreodinger method of the molecular orbitals – a linear combination of atomic orbitals (MO LCAO).

Yang Zhang et al. researches resulted in tumor regrowth after chemotherapy with fluorouracil which suppress immune system [12]. Authors have proclaimed conclusion, that damages immune system leads to tumor regrowth.

O. Connell M.J. et al. (13) and Luo J. et al (14) studied patients with colon cancer of stage II/III after treatment with surgery alone or surgery plus chemotherapy fluorouracil plus leucovorin and received results that tumor was removed in first event and recurrence cancer in second events [13,14].

Kast R.E. et al. studied treatment approach with nine cytotoxic drugs for research of relapsed Glioblastoma (15) and received accelerated growth of Glioblastoma [15].

Gifford J.B. et al. studied treatment Pancreatic ductal Adenocarcinoma and result in expression GRP78 protein induced resistance chemotherapeutic treatment which leads to relapsed tumor [16].

Thus researches Yang Zhang et al., Luo J. et al., O. Connell M.J. et al., Kast R.E. et al., Gifford J.B. et al. have not considered as targets of cytotoxic drugs operations on oncologic viral [v-oncogene] driving mechanisms in causing relapsed cancer disease as well as interactions between oncologic viruses, hormonal system and immune system of an organism in processes resistance to cytotoxic drugs and process of relapsed cancer disease. Just target of chemotherapeutic treatment with cytotoxic drugs affect nuclear DNA (nDNA) suppressing as G1/S/G2 phases cancer cellular cycle as well as Meiosis-Mitosis phase cancer cellular cycle which touch on as oncologic viral [v-oncogene] prokaryotic genome as well as human eukaryotic genome. It is occurred resistance between antiviral force of cytotoxic drugs and oncologic viral [v-oncogene] force for survival in which transition Meiosis-Mitosis into Mitosis-Meiosis reflects prevalence antiviral forse in which viruses [v-oncogenes] use rest hormonal mechanisms (not damaged by cytotoxic drugs) for supporting cancer cells development via accelerating cellular cycle [2,4]. Just retaining Meiosis-Mitosis cancer cellular cycle of survived oncologic viruses [v-oncogenes] uses also accelerating cancer cellular cycle which is supported by rest hormonal mechanisms of some hormones activity after some time of intensive cytotoxic drugs treatment. Thus rest hormonal glands of some hormones activity and immune T memory cells, T helper cells, T killer cells with B cells are restored after some time of intensive cytotoxic drugs treatment in which hormones restore activity of immune T memory cells, T helper cells, T killer cells. The immune T memory cells learn molecule of cittotoxic drug into hormonal gland's cells injured by cytotoxic drugs. Then T memory cells transmit the data of cytotoxic drugs molecules to T helper cells and further to T killer cells. The T killer cells destruct the molecule of cytotoxic drugs causing resistance to the anticancer activity of drugs. Besides it gives possibility some survived oncologic viruses [v-oncogenes] to create relapsed cancer disease after some time of intensive cytotoxic therapy. However some molecules of cytotoxic drugs don't leave data of theirs genomes in substances of injured cells of hormonal glands, and T memory cells don't learn their molecules. Therefore these cytotoxic drugs are not subjected to destruction of their molecules by T killer cells. Thus there are not resistance to anticancer activity of these cytotoxic drugs.

Discussion mechanisms sensitivity and resistance to some cytotoxic anticancer drugs as well as relapsed cancer disease after cytotoxic therapy

The mechanisms recurrence cancer disease was described by authors in following mode. The some authors noted that suppression by great dosage cytotoxic drugs of cells immune system cause recurrence cancer disease after cytotoxic chemotherapy. The other authors noted that unsufficient or unefficient chemotherapy leads to relapsed cancer disease. However it must be considered the interactions between restoring of depressed oncologic virises [v-oncogenes], restoring of some depressed immune system and restoring of some depressed hormonal system after intensive chemotherapy with cytotoxic drugs [2, 4, 17-20]. Just the affected by viral DNA [v-oncogene], the human cells' DNAs are subjected to viral accelerated cellular cycle via forming cancer combined Meiosis-Mitosis phase of cancer accelerated cellular cycle which are arisen by shift balance anabolic anaerobic endergonic processes & catabolic anaerobic exergonic processes into the excessive anabolic anaerobic endergonic processes of increased biosynthesis of proteins in G0 and G1 phases cellular cycles which cause abundance consumption energy and acetyl coenzyme A [Acetyl-CoA] leading to overloaded "nodal point of bifurcation anabolic and catabolic processes [NPBac]" because of insufficient energy and Acetyl-CoA and causing partial suppression catabolic anaerobic exergonic processes of Krebs tricarboxylic acid cycle [TCA] (21) (Figure 3). Just excessive quantity Lactic acids accumulate energy for excesive anabolic processes in cancer metabolism (Figure 3) [21]. The overloaded "nodal point of bifurcation anabolic and catabolic processes [NPBac]" because of insufficient energy and Acetyl-CoA and partial suppression catabolic anaerobic exergonic processes of Krebs tricarboxylic acid cycle [TCA] create obstacle for excretion from cancer cells of waste high-molecular substances as products of excessive

anabolic biosynthetic processes. Therefore cancer cells via their resonance waves of cellular capacitors find healthy tissues without overloaded "nodal point of bifurcation anabolic and catabolic processes [NPBac]" and move due to remote reactions between cancer cells and this tissue causing attraction into these tissues forming metastases (Figure 3) [21,22].

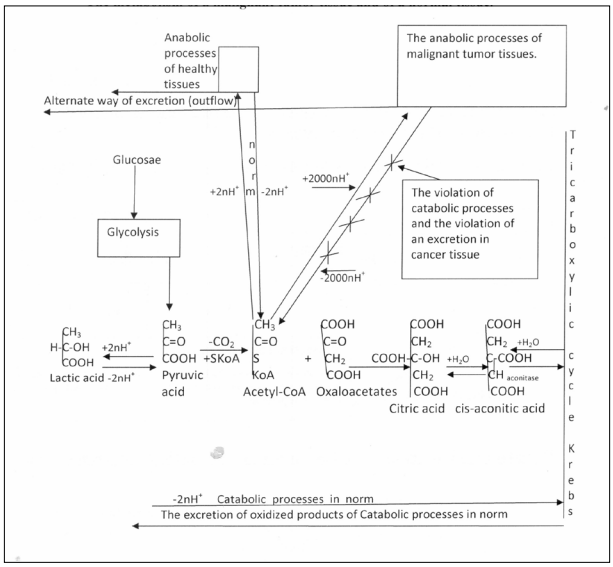

Figure 3: The mentabolism of a malignant tumor tissue and of a normal tissue

The suppression catabolic anaerobic exergonic processes of Krebs tricarboxylic acid cycle [TCA] leads to shift balance catabolic anaerobic exergonic processes & catabolic aerobic exergonic oxidative processes into expression catabolic aerobic exergonic oxidative processes. Thus it forms both excessive anabolic anaerobic endergonic processes and expression catabolic aerobic exergonic oxidative processes. The excessive anabolic anaerobic endergonic processes and expression catabolic aerobic exergonic oxidative processes display Warburg effect mechanism of "aerobic glycolysis in cancer tissue" versus Pasteur effect of incompatibility glycolysis and aerobic oxidation in healthy tissue" (Figure 4) [21-24].

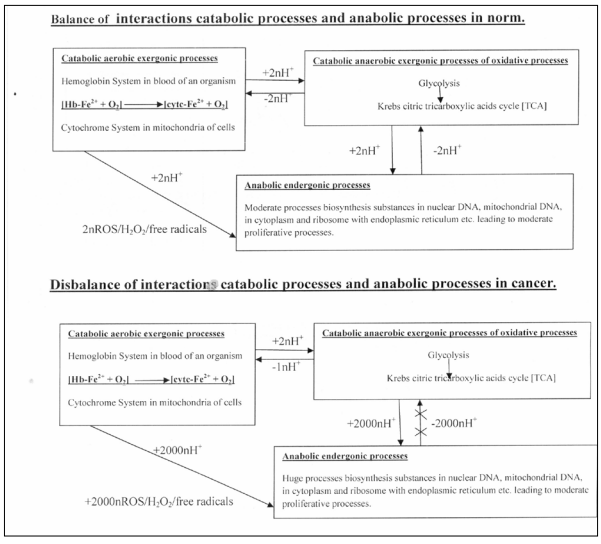

Figure 4: Influences of energy flow on interactions catabolic processes and anabolic processes in norm and in cancer pathology

The active chemotherapy with great dosage cytotoxic drugs suppress as cancer cellular cycle as well as immune system mechanisms and hormonal system mechanism causing some violation maintenance stability Internal Energy of an organism [25, 26]. Just the target of chemotherapeutic treatment with cytotoxic drugs is nuclear DNA (nDNA) causing suppression as G1/S/G2 phases cancer cellular cycle as well as Meiosis-Mitosis phase cancer cellular cycle which touch on as viral prokaryotic genome as well as human eukaryotic genome. After some time cessation of chemotherapy or some weakening chemotherapy it is occurred restoring hormonal glands activity via production hormones which stimulate cellular capacitors operation of an organism's immune cells, especially immune cells of T lymphocytes and B lymphocytes operations resulting in gradual recovery Internal Energy of an organism. Simultaneously it is occurred restoring cells cellular capacitors, affected by viral oncogenes [v-oncogenes]. Further it is happened resistance between antiviral force of cytotoxic drugs and viral oncogenes [v-oncogene] force for their survival in which transition Meiosis-Mitosis into Mitosis-Meiosis reflects prevalence antiviral force of cytotoxic drugs. But retaining Meiosis-Mitosis reflects prevalence viral force for viral survival in which viruses [v-oncogenes] use rest hormonal mechanisms (not damaged by cisplatin) for supporting cancer cells development via accelerating cellular cycle (2, 4). Just retaining Meiosis-Mitosis cancer cellular cycle, causing survived oncologic viruses [v-oncogenes], exerts accelerating cancer cellular cycle which is supported by rest hormonal mechanisms of hormones activity after some time of intensive cytotoxic drugs treatment. Thus it gives possibility some survived oncologic viruses [v-oncogenes] which create relapsed cancer disease after some time of intensive cytotoxic therapy. Besides rest hormonal glands exert hormones activity and immune T memory cells, T helper cells, T killer cells with B cells which are restored after some time of intensive cytotoxic drugs treatment in which hormones restore activity of immune T memory cells, T helper cells, T killer cells. The immune T memory cells' resonance waves of T memory cells cellular capacitors operations learn molecule of cytotoxic drug as strange substance into hormonal gland's cells injured by this cytotoxic drug. Then the data of the cytotoxic drug molecule is transmited from T memory cells to T helper cells because resonance waves of T helper cells' cellular capacitors react on strange drug's molecule into T memory cells, and further the data of the cytotoxic drug molecule is transmited from T helper cells to T killer cells because resonance waves of T killer cells' cellular capacitors react on strange drug's molecule into T helper cells. The T killer cells destruct the molecule of cytotoxic drug causing by enzymes of their lysosomes due to resonance waves of their capacitors operation corresponing to the wave functions molecule orbitals of cytotoxic drugs' substances corresponding to the method molecular orbitals – a linear combination of atomic orbitals (MO LCAO), according outstanding Schreodinger equaton (Figure 2) [17]. There are occurred the reaction resonance waves on the cytotoxic drugs as the strange substances that cause attraction cytotoxic drug as Ligant to the variable capacitors of the Receptors on the walls of immune cells (Figure 2) [17]. It forms link Receptor-Ligant. Then it is occurred internalization Receptor-Ligant into cell due to resonance waves of cellular capacitors operation. The chemical potentional of drug's substances change stable basophilic chemical potential of Cytoplasm ($\mu_{cytopl.}$), i.e. change Internal Energy of T cell. The changed T cells' stable basophilic Internal Energy leads to violation cellular balance anabolic processes & catabolic anaerobic processes & catabolic aerobic processes that exerts reactions capacitors of nuclear shell, capacitors of mitochondrial shells, capacitors of ribosomal shells, capacitors of lysosomal shells and capacitors the other Organeles for restoration stable cellular basophilic chemical potentials of cytoplasms T cells and B cells. The dissolved of drug's substances in T memory cells' cytoplasms cause contacts drug's

substances with Nucleus, Mitochondria, Ribosomes, Lysosomes and the other Organelles substances in which T memory cells learn wave function molecules orbitals of cytotoxic cells. Thus it is occurred sensitized T memory by cytotoxic drugs. Again appearance cytotoxic drugs exert immune reaction of resonance waves of T memory cells' cellular capacitors which stimulate reactions of T helper cells by resonance waves of variable cellular capacitors. Then T killer cells, being sensitized by T helper via their resonance waves of cellular capacitors, destroy drugs' substances promoting attraction Lisosomes to the drugs for decomposing drug substances by lisosomal enzymes. Thus immune system of T cells realize resistance to cytotoxic drugs by the immune reaction of sensibilized immune T cells of an organism via link T memory cells → T helper cells → T killer cells causing reaction on strange substances of wave function of cytotoxic drugs' molecule orbits resulting in resistance to the cytotoxic drugs' influences. Thus it is happened the resistance to the anticancer activity of cytotoxic drug. On the other hand, some molecules of cytotocsic drugs don't leave data of theirs genomes in substances of injured cells of hormonal glands, and T memory cells don't learn their molecules. Therefore these cytotoxic drugs are not subjected to destruction of their molecules by T killer cells. Thus there are not resistance to anticancer activity of these cytotoxic drugs.

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