Chemodrug resistance: Cancer's fight for survival

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Abstract

Introduction. Chemoresistance is a multifactorial phenomenon implicated in all failed therapies and accounts for 90% of all cancer deaths and 30% of relapses. **Objective**. To understand the genetic mechanisms by which cancer cells acquire resistance to chemo drugs. **Methodology**. A non-systematic review study was carried out, in which genes and proteins involved in chemoresistance were searched using the terms "Cancer Drug resistance [Title/Abstract]". From the articles obtained, highly involved genes, emerging genes, and proteins related to resistance were recognized. To obtain more specific information about genes, their interactions, and proteins associated with metabolism, the tools "The Human Protein Atlas", "STRING CONSORTIUM 2022," and The Small Molecule Pathway Database were used for their review. **Results**. From this review it was found that there are genes highly related to resistance such as: *ABCA3, ABCB1, ABCB2, ABCC1, ABCC2, ABCG2, CYP2D6, CYP3A4, GSTA1.* Recently recognised genes such as*: FOXO3, FOXM1, Skp2, Snail, Twist1, ZEB1* and *SLCO1B3*. **Conclusions**. It is necessary to taking account new approaches related to cancer treatments considering chemoresistence and the genes related to the resistance.

Keywords: cancer, resistance, chemoresistance, cytochrome P450.

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Introduction

In 2020, cancer was the leading cause of death worldwide, with close to 10 million deaths, with lung cancer being cancer with the highest incidence in men, with 31.5 cases per 100,000 men worldwide. breast cancer in women with 47.8 cases per 100,000 women, and leukemia in children under 19 years of age had 3.2 new cases per 100,000 individuals (1). According to a 2020 study by Bukowski k. *et al* ., estimate that at least 90% of cancer deaths are due to patients' resistance to treatment (2). It is estimated that by 2040, there will be 26 million new cancer cases worldwide, and approximately 15 million patients will require chemotherapy (3). Therefore, it is essential to have more effective treatments against cancer, in which new approaches are considered that adopt the influence that chemoresistance can have and how it affects the success of therapy against this disease.

Chemoresistance occurs when cancer cells are more tolerant to treatment; with the outcome of therapeutic losses effect. The bases of chemoresistance lies in different molecular mechanisms, one of the well described is the efflux pumps corresponding to the family of ATP-Binding Cassette (ABC) genes. These genes codify for ABC proteins wich transports small molecules, including chemo drugs, outside the membrane. Other of the main mechanisms is

drug metabolizm through to the cytochrome p450 (CYP450) superfamily. (4,5).

Recently, cancer treatments have been based on the administration of regimes of more than two drugs at long-term and high doses. The drawback of the long and intensive treatments is the possibility of acquire treatment resistance, resulting in a higher mortality rate and cancer relapses. The focus of this review is to understand how cancer cells acquire resistance to chemopharmaceuticals.

Methodology

In order to retrieve the most relevant information related to the subject, the National Center for Biotechnology Information (NCBI) database, The Human Protein Atlas (https://www.proteinatlas.org/) and STRING CONSORTIUM 2022 were used. (https://string-db.org/).

To obtain information related to the history of chemoresistance, we searched for the PubMed.gov search engine (https://pubmed.ncbi.nlm.nih.gov/), using the words "Drug resistance", we further analyzed detailed the oldest articles that the search yielded, also in this section the Google Scholar search engine was used to search information related to Dr. Paul Ehrlich, the information was acquired according to the interest of continuing to search for relevant ideas at the beginning of the resistance to drugs.

For the rest of the sections, the PubMed. gov search engine was used by introducing the word "Cancer Drug resistance [Title/Abstract]", these were limited to their appearance in the title and abstract, thus obtaining 1,042 results. , then they were filtered as follows: in text availability, free and complete texts were selected; In type of article, review, books, and documents were selected; On the date of publication, the years 2017 to 2022 were selected, obtaining 198 results. We applied additional filters to these results: only in humans and English as a language, getting 69 results. The information of the articles related only to cancer in general and not to other diseases or any type of article was acquired, thus obtaining a total of 36 articles.

To search for information related to chemopharmaceuticals, the name of the chemopharmaceuticals was introduced in the search engine, and the articles related to it were selected.

Cell location

Protein visualization at the cellular level was performed using The Human Protein Atlas database (https://www.proteinatlas.org/).

Drug metabolic pathways

Enzymes retaled to metabolizm of each drug were obtained from The Small Molecule Pathway Database (SMPDB; https://smpdb.ca/). A total of 11 meatabolic pa-

thway related to anticancer drugs and paracetamol were obtained.

History of resistance to chemo pharmaceuticals

The meaning of "drug resistance" could be analyzed in two concepts. In one way the term "drug", refers to a set of molecules that help treat a disease or condition; the drug is made up of the active molecule or ingredient and a presumably inert excipient. In the other way "resistance" is associated with the property of tolerating conditions outside the optimal operating range. Collectively, drug resistance is when cancer cells or microorganisms, do not respond to a drug that usually weakens or destroys them. Drug resistance occurs before, during, or after administering the treatment (6)

The origin of drug resistance is not completely clear, however, we can dated its beginnings with the contributions of the German beginning with the contributions of the German doctor and bacteriologist, Paul Ehrlich, who was awarded the Nobel Prize in medicine in 1908. In addition to his contributions in the discovery of arsphenamine, the first effective medicinal treatment against syphilis, in 1878 he published the theory of selective toxicity, in which Paul Ehrlich mentions that staining is selective of biological tissues, due to specific chemical characteristics of cells and

in 1906 he coined the term chemotherapy (7–9). Later in 1916, the scientist Seinai Akatsu of the Rockefeller Institute publi-shed an article entitled "The drug-fastness of spirochetes to arsenic, mercurial, and io-dide compounds *in vitro* ", in which he des-cribed the following: "it has been known for some time While in trypanosomiasis, trypanosomes that have survived the first effect of an arsenic germicide, such as atoxyl or arsacetin, offer greater resistance to a subsequent dose of the same drug" , with the latter we can say that knowledge of the effect (10)of drug resistance is more than 100 years old, remembering that the first treatments against different diseases date from the use of medicinal compounds after the contributions of Paul Ehrlich. An important event of the last century was the establishment of the HeLa cell line derived from a squamous cell carcinoma of the cer-vix, being the first cancer cells that have contributed to the pharmacological study of chemical compounds, despite this, today the chemoresistance continues to affect the efficacy of drug treatments (7,11–14).
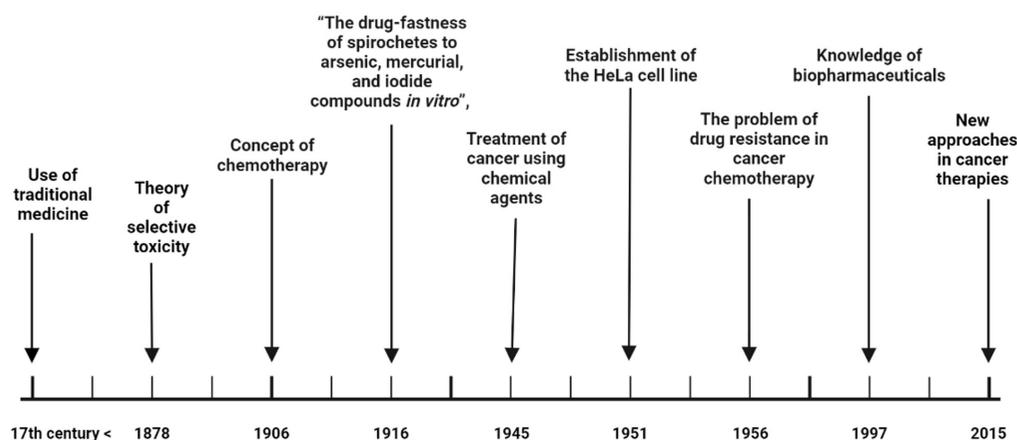
Figure 1. Chemoresistance time line.

Chemopharmaceuticals and their resistance mechanism

Cancer treatments are based on the admi-nistration of multidrugs (4 to 6) at diffe-rent concentrations, which are selectively directed for different molecular targets; the drugs are employed depending on the severity and the stage of the disease, for example, treatments for acute lympho-blastic leukemia consist of a combination of genotoxic drugs, antimetabolites, mito-tic spindle inhibitors, and glucocorticoids (GCs) (15). Treatments usually consist of three phases: Remission induction; Conso-lidation/intensification, maintenance (16).

There are different chemo pharmaceuticals, which can be classified depending on the molecular target; among these, we have: alkylating agents such as oxazsafosforinas, nitrogen mustards, hydrazine, platinum-based agents, there are also antimetabolite agents such as pyrimidine antagonists, antagonists of purines, purine analogs, antifolates, and ribonucleotide reductase inhibitors. There are some spindle inhibitors like taxane and some vinca alkaloids, there are also topoisomerase I and II inhibitors (2).

One of the most used chemopharmaceuticals is doxorubicin (Dox), it is an antibiotic belonging to the anthracycline family, extracted from the bacterium *Streptomyces peucetius* , the use of Dox as a drug against cancer was started in the fifthys years. Dox is a DNA intercalator, by being located between the DNA chain, it prevents the topoisomerase II enzyme from carrying out replication, making in the first instance that the cancer cell cannot replicate and in turn, prevents the transcription of genes necessary for the cell, for this reason, the cancer cell dies. Despite its efficiency in treating solid and blood tumors, it has been seen that patients acquire resistance against the drug, and it has also been associated with hepatic, renal, and cardiac cytotoxicity (5,17). Another drug widely used in cancer is tamoxifen; this chemo pharmaceutical is a selective modulator of the non-steroidal antineoplastic estrogen receptor. Tamoxifen competitively inhibits estradiol by binding to estrogen receptors, thus, preventing, thus preventing the receptor from binding to the estrogen response element in DNA. The result is a reduction in DNA synthesis and the cellular response to estrogen (18). However, drug resistance to tamoxifen is also known to exist (17,19). Cisplatin is an antitumor drug widely used to treat various types of cancer. Despite its remarkable efficacy, most tumors show intrinsic or acquired resistance to this drug. The main biological target of cisplatin is genomic DNA, causing many DNA lesions that block transcription and replication (17,20).

Resistance to chemotherapeutics is on the rise, with more and more individuals with resistance profiles to different drugs, making cancer therapies inefficient (21).

Before understanding the mechanisms by which cancer cells develop resistance to chemopharmaceuticals, it is necessary to understand that tolerance refers to cells' ability to survive transient exposure to a chemical agent. On the other hand, we have that persistence is the capacity of a clonal subpopulation to survive to the treatment(22); for example, suppose there are 100 cells in a culture to which a therapeutic agent *x* is administered, after some time (t=1), it is performed a cellular count obtaining ten cells, so it could be said that each cell had tolerance to the therapeutic agent, then another count is performed at t=2 with the same culture conditions, coun-

ting 20 cells, the ten cells presented before and their descendence; therefore, this new clonal subpopulation was persistent to the treatment, since the concentration of drug x will no longer have a therapeutic *effect*. The above approach is mainly used with microorganisms, but it helps us understand the effect of cell resistance.

It is currently considered that a cancer disease can contain cancer cells that are sensitive or resistant to drugs, so the two states are not mutually exclusive, both occurring at the same time. Resistance, whether intrinsic or acquired, is irreversible and arises from the accumulation of alterations in cancer cells or their tissue microenvironment, with the sole objective of promoting cancer cell survival. Intrinsic resistance is associated with pre-existing (inherited) genetic mutations which are heterogeneous among cancer cells from the same individual. Pre-existing unresponsive cell subpopulations will be selected after drug treatment, resulting in the activation of intrinsic pathways used as a defense against environmental toxins. After drug treatment, acquired resistance may appear (22,23). We can see chemoresistance from the point of view of evolution, cancer cells, like any other organism, constantly evolve for survival, developing mechanisms to adapt to the environment's adverse conditions. Cancer is a chronic degenerative disease, where cells divide uncontrollably, despite this, cancer cells are highly adaptable, evolving to sur-

vive, it is possible that we can take advantage of some mechanisms of cancer cells and use them rationally in favor of our survival. Some of the most common cellular and molecular resistance mechanisms in cancer are listed below.

Molecular target modification

This mechanism is mediated by molecular target changes, these changes involve sites of drug binding, and thus the new molecular sites cannot be recognized by the drug. In the case of proteins as molecular targets, a genetic mutation causes the protein to change its conformation, or the site for which the drug was designed, causing loss of affinity for the target site (2,4,24,25).

Production of metabolizing or biotransforming enzymes

Biotransformation is a method that cells use so that drugs can be more easily excreted and this process is generally carried out in two phases. Phase I biotransformation is primarily mediated by cytochromes P450 (CYPs) and, to a lesser extent, flavin-containing monooxygenases. This phase is associated with reduction reactions. Phase II biotransformation involves a larger number of families of enzymes, including UDP- glucuronosyltransferases (UGT), sulfotransferases, N-acetyltransferases, and glutathione S-transferases (GST); this process is based on conjugation reactions (26). The resistance mechanism is based on the

overexpression of these metabolizing enzymes, which have been found to increase their expression, especially the enzymes of the CYP540 family, the GST superfamily, the UGT superfamily, gamma-glutamyl transferases and thiopurine methyltransferases (2,4).Recently, the importance of amino acid metabolism in chemoresistance has been discussed, because amino acids help cancer cells counteract therapies by maintaining redox homeostasis, supporting biosynthetic processes, regulating epigenetic modification, and providing metabolic intermediaries for cell metabolism. (27).

Tumor microenvironment

It is well known that the environment in which cancer cells develop is highly heterogeneous, enriched by extracellular signals that stimulate signaling pathways involved in metabolism, cell division, cell remodeling, and the production of transcription factors. These signals are made up of different molecules, among which we have hormones, cytokines, and interleukins (IL) such as IL-1, IL-4, IL-6, and IL-8; there are also different growth factors such as FG2, FGF9 and FGF10, all these molecules are secreted into the environment by secretory cells, lymphocytes, and fibroblasts generally. Additionally, the extracellular matrix is a three-dimensional network that provides structural and biochemical support to cancer cells, being an important component in the tumor microenvironment. (2,4,23,28–31). Also, cancer cells can produce vesicles

containing molecules such as microRNA (miRNA) or messenger RNA (mRNA) inside, which can promote chemoresistance. It has been observed that extracellular vesicles are involved in processes such as stromal activation, angiogenesis, evasion of the immune system, reprogramming of energy metabolism, transfer of mutations and metastasis, thus, extracellular vesicles can modulate the tumor microenvironment in favor of the resistance (32–37).

Efflux pumps

Membrane cell have proteins that function as channels, which allow the passage of small molecules and ions. Efflux pumps are protein complexes that push drugs out of the cell, preventing the drug from carrying out its therapeutic effect. The efflux pumps belong mainly to the ABC transporter superfamily, of which there are 7 families (ABCA-ABCG) with 48 members in total. But only the ABCB1, ABCC1 and ABCG2 members are the ones that have seen to be involved with resistance to chemopharmaceuticals (2,4,38).

Epigenetics

Epigenetics is the study of changes that activate or inactivate genes without changing the DNA sequence, due to age and exposure to environmental factors (diet, exercise, medications and chemicals). Epigenetics refers to a non-genetic cellular memory, which records environmental and

developmental cues (and alternative cellular states in unicellular organisms), is the basis of epi-(above)-genetics (39,40). Resistance is related to DNA methylation, histone modification, chromatin remodeling, and non-coding RNA related alterations (2,4,41,42). Histone deacetylase 3 (HDAC3) belongs to the group of genes associated with cancer and has been implicated as a regulator of responses to anticancer drugs, angiogenic potential, and tumorigenic potential (43).

Coding and non-coding RNA

Messenger RNA (mRNA) is the coding sequence of each gene, it is the sequence that is translated into protein, and resistance is associated with modifications that this sequence can undergo, this sequence changes could modify some basic cellular proceceses, such as, alternative splicing, the modification of adenosine to inosine (A to I) and mRNA methylation (44). On the other hand, we have the resistance mechanisms related to miRNAs. miRNAs are short which are short (20-24 nt) non-coding RNAs that participate in the post-transcriptional regulation of gene expression in multicellular organisms by affecting both the stability and the translation of the mRNAs. Recently, some miRNAs expression have been associated to chemopharmaceuticals resistance, these miRNAs are expressed by cancer cells and it has been seen that these are independent of the type of cancer. For example, miR-100, miR-222, miR-30a and miR-17 were found in breast cancer (32,45–47). Other non-coding RNAs such as long non-coding RNAs (LncRNA), circular RNAs (CircRNA) have also been associated with the development of resistance (44).

Genes and proteins related to chemo resistance

As we have already seen, there are certain mechanisms by which cells can evade the therapeutic effect of chemopharmaceuticals and these mechanisms may be due to gene-protein or protein-protein interactions, this interections could result in activation, inhibition or lost of function. These interactions can form positive or negative feedback loops, stimulation leading to an effect, which cyclically promotes the stimulus again.

The STRING database alone contains 67,592,464 proteins belonging to 14,094 organisms, of which it is estimated that they can form approximately 20,052,394,041 total interactions, including low-confidence interactions (48). Despite all these proteins and interactions that can take place, only some proteins are strongly related to chemoresistance, such as the ATP-binding cassette subfamily protein member three encoded by the *ABCA3* gene (gene *ID*: 21); the entire transporter encoded by this gene may be involved in xenobiotic resistance development and the programmed uptake during programmed cell death.

ATP-binding cassette subfamily B member one Protein is multidrug resistance-related protein, encoded by the *ABCB1 gene* (gene ID: 5243); this protein is an ATP-dependent drug efflux pump for xenobiotic compounds with broad substrate specificity. Transporter 1 protein, a member of the ATP-binding cassette subfamily B encoded by the *ABCB2 gene* (gene ID: 6890), is involved in pumping degraded cytosolic peptides across the endoplasmic reticulum to the membrane-bound compartment where class I molecules are assembled. The ATP-binding cassette subfamily C member 1 protein encoded by the *ABCC1 gene* (gene ID: 4363), is a transporter member of the MRP subfamily that is involved in the multidrug resistance. The ATP-binding cassette subfamily C member 2 protein encoded by the *ABCC2 gene* (gene ID: 1244), this transporter is substrated with anticancer drugs such as vinblastine; therefore, this protein appears to contribute to drug resistance in mammalian cells. ATP-binding cassette subfamily protein G member 2, known as breast cancer resistance protein, functions as a xenobiotic transporter encoded by the ABCG2 gene (gene ID: 9429) . Cytochrome P450 enzyme family two subfamily D member 6, this protein is located in the endoplasmic reticulum and is known to metabolize up to 25% of commonly prescribed drugs; its substrates include antidepressants, antipsychotics, analgesics and cough suppressants, beta-adrenergic blockers, antiarrhythmics, and antie-

metics, it is encoded by the *CYP2D6 gene* (gene ID: 1565). The cytochrome P450 has a family of three subfamilies. A member four enzyme encoded by the *CYP3A4 gene* (gene ID: 1576), has been implicated in the metabolism of approximately half of the drugs in use today, including acetaminophen, codeine, cyclosporine A, diazepam, erythromycin, and chloroquine. The enzyme glutathione S-transferase alpha one, encoded by the *GSTA1 gene* (gene ID: 2938), catalyze the glutathione addition to an electrophilic target, the targets include, carcinogens, therapeutic drugs, environmental toxins, and products of oxidative stress (32,38,42,44,45,49,50).

Figure 2 shows the intracellular localization of proteins related to resistance to chemopharmaceuticals, such as cytochrome P450 enzymes, some monooxidases, and enzymes from the uridine diphospho-glucuronosyltransferase superfamily (see Fig. 3).
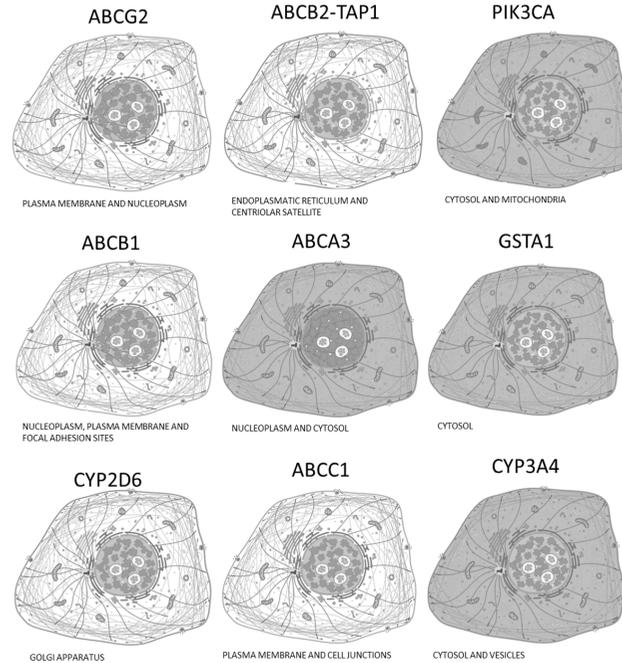
Figure 2. Cellular localization of the proteins encoded by the resistance genes. The gray colored sites are the cellular localization of the protein.

Gene	Main interaction gene	Score (0 al 1)
ABCA3	ADNJC6	0,844
ABCB1	CYP3A4	0,964
ABCB2	TAP2	0,998
ABCC1	ABCG2	0,932
ABCC2	PDZK1	0,956
ABCG2	ABCC1	0,932
CYP2D6	MAOA	0,955
CYP3A4	UGT2B7	0,981
GSTA1	GSTA2	0,963

Edge Confidence
- low (0.150)
- medium (0.400)
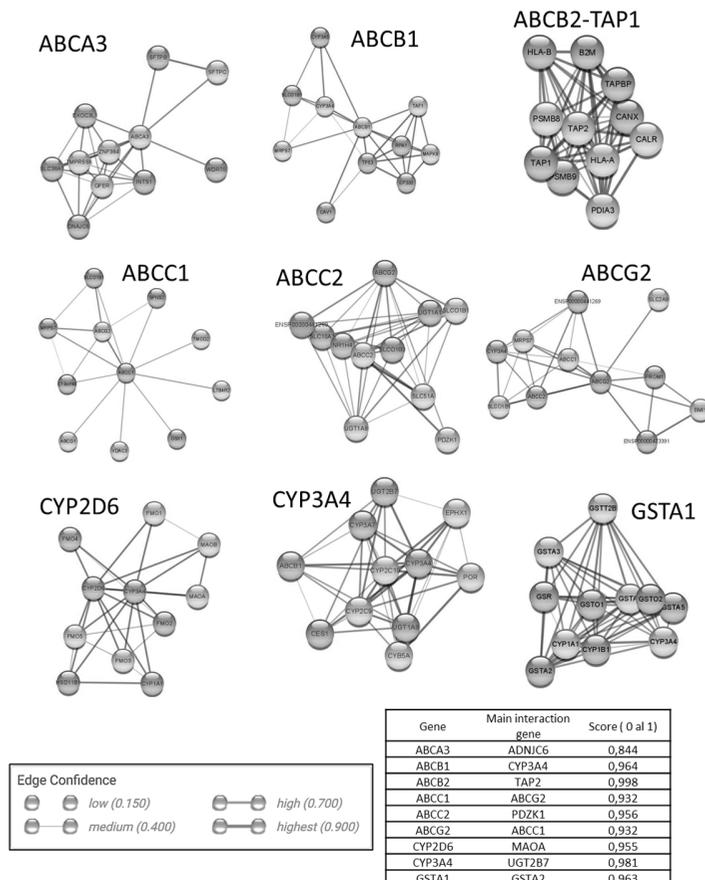- high (0.700)
- highest (0.900)

Figure 3. Interactomes of the proteins encoded by the resistance genes with other proteins.

Recently there are studies that suggest other genes and proteins that are related to chemoresistance's, such as the transcription factors FOXO3 and FOXM1, which participate downstream in the PI3K-Akt, Ras-ERK, and JNK/p38MAPK signaling cascades. , these pathways are crucial for cell proliferation, differentiation, cell survival, senescence, DNA damage repair, and cell cycle control (50,51). Also, it has been seen that human aldo-keto reductase (AKR) enzymes catalyze the NADPH-dependent reduction of carbonyl groups to alcohols and participate directly in the metabolism of chemopharmaceuticals, contributing to chemoresistance (17). It has been found that S-phase kinase-associated protein 2 (Skp2) and E3 ligase are highly correlated with chemoresistance, and high expression of these proteins is associated with a poor prognosis in Her2-positive patients (52). Another important group that has been found to be related to chemoresistance is the group of heat shock proteins (HSPs), which may act as an upstream regulator of oncogenic pathways related to tumorigenesis, metastasis, and invasiveness in various types of cancer, cancer. HSPs proteins contributes to the progress of the disease and more specifically activate signaling pathways and genes related to chemoresistance (53). F-box proteins (FBPs) play a fundamental role in developing drug resistance through ubiquitination and degradation of substrates (54). *Snail* , *Twist1* , and zinc-finger E homeobox-binding 1 (*ZEB1*) genes

orchestrate gene expression that mediates the transition from epithelial cells to mesenchymal cells, implicating cancer development and metastasis and are also related to resistance to medications (55). Intracellular cholesterol accumulation in cancer cells, promotes drug resistance and allows these cells to evade apoptotic signaling processes and maintain cell division and proliferation; also, lipid metabolism is implicated in resistance to chemopharmaceuticals (56,57). Insulin-like growth factor 1 (IGF-1) is known for its role in supporting cancer progression and metastasis through the promotion of neovascularization in transforming tissues and the promotion of proliferation, maintenance, and migration of malignant cells. A growing number of reports support that IGF-1 fuels tumorigenesis and induces the development of resistance to anticancer drugs (58). The solute transporter 1B3 (SLCO1B3) member of the organic anion transporters is a transporter normally expressed in the liver, transporting a variety of endogenous and exogenous compounds, including hormones and their conjugates. The extrahepatic expression of SLCO1B3 has been detected in different cell lines and cancer tissues. Recently, accumulating data indicates that abnormal expression and function of SLCO1B3 are involved in anticancer drug resistance (49,59).

It has been observed that resistance-associated proteins are highly related to proteins involved in drug metabolism, and

alteration in the sequence of these genes or overexpression is related to chemoresistance. Certain mutations in the CP540 superfamily enzyme-coding genes cause individuals to be slow, rapid, or super-rapid metabolizers of certain drugs, rendering therapies less effective for extensive metabolizers, and vice versa. Slow metabolizers are more susceptible to have a toxic effect, these effects depend on the type of drug being administered and the disease being treated (26). Table 1 describes some chemopharmaceuticals used in cancer therapy and the proteins related to their metabolism, the proteins involved in the metabolism of paracetamol are also shown . Paracetamol is an effective analgesic and antipyretic for the control of mild or moderate pain caused by joint conditions, ear pain, headaches, odontogenic pain, neuralgia, minor surgical procedures, among others. This drug is prescribed to people regardless of age or sex. There are proteins that may be involved in the metabolism of more than one chemopharmaceutical drug, such as the enzymes of cytochrome P450 3A4, and cytochrome P450 2B6; there are also efflux pumps, such as the protein of ATP-binding cassette subfamily G member 2. This multiple substrates for some proteins is not surprising; but; it is interesting the number of proteins involved in the metabolism of chemo pharmaceuticals and the metabolism of paracetamol. Due to its high medical prescription, it is believed that paracetamol is harmless in the body; however, as it is related to the response to a large number of genes related to chemoresistance, it suggests that this drug, and probably all the drugs we consume today every day in our lives, may contribute to resistance without realizing it, even knowing that sometimes we require higher doses to counteract a condition that we could previously alleviate with a low dose.

Table 1. Proteins involved in the metabolism of some anticancer drugs.

Etoposide(60)	Mercaptopurine(60)	Cyclophosphamide(60)	Teniposide(60)	Ifosfamide(60)	Capecitabine(60)
Multispecific canalicular transporter of organic anions 2	Adenosine kinase	Aldehyde dehydrogenase, dimeric with a preference for NADP	Cytochrome P450 3A4	Aldehyde dehydrogenase, dimeric with a preference for NADP	Cytidine deaminase
Cytochrome P450 3A4	Aldehyde oxidase	Cytochrome P450 2A6	Cytochrome P450 3A5	Cytochrome P450 2A6	Hepatic carboxylesterase 1
Cytochrome P450 3A5	ASmidophosphoribosyl-transferase	Cytochrome P450 2B6	DNA topoisomerase 2-alpha	Cytochrome P450 2B6	Sodium/Nucleoside Cotransporter 1
DNA topoisomerase 2-alpha	Equilibrium nucleoside transporter 1	Cytochrome P450 2C19	Myeloperoxidase	Cytochrome P450 2C8	Thymidine phosphorylase
DNA topoisomerase 2-beta	Equilibrium nucleoside transporter 2	Cytochrome P450 2C8		Cytochrome P450 2C9	Thymidylate synthase

Etoposide(60)	Mercaptopurine(60)	Cyclophosphamide(60)	Teniposide(60)	Ifosfamide(60)	Capecitabine(60)
Multidrug resistance protein 1	GMP synthase [glutamine hydrolyzation]	Cytochrome P450 2C9		Cytochrome P450 3A4	
Myeloperoxidase	Hypoxanthine-guanine phosphoribosyltransferase	Cytochrome P450 3A4		Cytochrome P450 3A5	
Prostaglandin G/H synthase 1	Inosine-5'-monophosphate dehydrogenase 1	Glutathione S-transferase Mu 1		retinal dehydrogenase 1	
Prostaglandin G/H synthase 2	Protein 4 associated with multidrug resistance	retinal dehydrogenase 1			
UDP-glucuronosyltransferase 1-1	Protein 5 associated with multidrug resistance				
	Ras-related botulinum toxin C3 substrate 1				
	Sodium/Nucleoside Cotransporter 2				
	Solute transporter family 28 member 3				
	Thiopurine S-methyltransferase				
	Xanthine dehydrogenase/oxidase				

Irinotecan(60)	Doxorubicin(60)	Tamoxifen(60)	Gemcitabine(60)	Acetaminophen (Paracetamol)(60)
Multispecific canalicular transporter of organic anions 1	Alcohol dehydrogenase [NADP(+)]	Cytochrome P450 2B6	5'(3')-deoxyribonucleotidase, cytosolic type	ATP-binding cassette subfamily G member 2
Cholinesterase	Aldo-keto reductase family 1 member C3	Cytochrome P450 2D6	CTP synthase 1	Bile salt sulfotransferase
Cocaine esterase	ATP-binding cassette subfamily G member 2	Cytochrome P450 3A4	Deoxycytidine kinase	Cytochrome P450 1A2
Cytochrome P450 3A4	Multispecific canalicular transporter of organic anions 1	Cytochrome P450 3A5	Deoxycytidylate deaminase	Cytochrome P450 2A6
Cytochrome P450 3A5	Carbonyl reductase [NADPH] 1	Dimethylaniline monooxygenase [N-oxide former] 1	Equilibrium nucleoside transporter 1	Cytochrome P450 2D6
DNA topoisomerase 1	Carbonyl reductase [NADPH] 3	Dimethylaniline monooxygenase [N-oxide forming] 3	Nucleoside diphosphate kinase A	Cytochrome P450 2E1
Hepatic carboxylesterase 1	Multidrug resistance protein 1	Estrogen receptor	Ribonucleoside diphosphate reductase large subunit	Cytochrome P450 3A4
Multidrug resistance protein 1	Multidrug resistance-associated protein 1	Sulfotransferase 1A1	Ribonucleoside diphosphate reductase M2 subunit	Estrogen sulfotransferase

Irinotecan(60)	Doxorubicin(60)	Tamoxifen(60)	Gemcitabine(60)	Acetaminophen (Paracetamol)(60)
Multidrug resistance-associated protein 1	NAD(P)H dehydrogenase [quinone] 1	UDP-glucuronosyltransferase 1-10	Ribonucleoside diphosphate reductase subunit M2 B	Glutathione S-transferase P
Solute transporter member of the 1B1 family of organic anion transporters	NADH dehydrogenase [ubiquinone] iron-sulfur protein 2, mitochondrial	UDP-glucuronosyltransferase 1-4	Sodium/Nucleoside Cotransporter 1	Glutathione S-transferase theta-1
UDP-glucuronosyltransferase 1-1	NADH dehydrogenase [ubiquinone] iron-sulfur protein 3, mitochondrial		Solute transporter family 28 member 3	Multidrug resistance protein 1
UDP-glucuronosyltransferase 1-10	NADH dehydrogenase [ubiquinone] iron-sulfur protein 7, mitochondrial		Thymidylate synthase	Multidrug resistance-associated protein 1
UDP-glucuronosyltransferase 1-9	NADPH: cytochrome P450 reductase		UMP-CMP kinase	Protein 4 associated with multidrug resistance
	Nitric oxide synthase, endothelial			Protein 5 associated with multidrug resistance
	RalA binding protein 1			Sulfotransferase 1A1
	Family of solute transporters 22 member 16			Sulfotransferase 1A3/1A4
	Xanthine dehydrogenase/oxidase			UDP-glucuronosyltransferase 1-1
				UDP-glucuronosyltransferase 1-6
				UDP-glucuronosyltransferase 1-9
				UDP-glucuronosyltransferase 2B15

Therapies against resistance to chemo pharmaceuticals

Today there are a wide variety of cancer therapies; some could help evade resistance mechanisms such as intermittent treatment regimen and minimum dose necessary; this treatment is based on containing tumors at a fixed tolerable level to allow expansion of drug-sensitive cells at the expense of resistant ones. Another emerging therapy is polytherapy, which focuses on targeting a cancer-specific overactive transcription factor/regulator, in addition to containing the necessary chemo pharmaceuticals to fight cancer, trying to propose simultaneously targeting multiple dependencies that generate chemoresistance, hence hybrid drugs are born, which simultaneously target many points of signaling networks and various structures within a cancer cell (22,24,61). Also, monoclonal antibodies directed at the inhibition of signal transduction can be used to prevent the proli-

feration of cancer cells, such is the case of anti-HER2 antibodies such as pertuzumab (Omnitarg), panitumumab (ABX-EGF) and Cetuximab (Erbitux). , which are under evaluation in clinical trials (51). Tumor plasticity is a phenomenon in which cancer cells adapt to tumor microenvironment; it is possible to develop strategies directed to specific plasticity regulators in order to overcome or stop cancer progression (31). Today there is an enormous amount of information that can be used by mathematical models to make computational predictions using systematic and quantitative approaches, with the purpose of providing deeper insight into resistance mechanisms, generating new hypotheses, or suggesting promising treatment strategies . for future therapies (62).

Mitochondria are the central organelle for cellular energy supply, they can rapidly undergo dynamic changes and integrate cellular signaling pathways to provide bioenergetic and biosynthetic flexibility to cancer cells; thus, mitochondria contribute to multiple aspects of cell characteristics. tumor, including drug resistance. To combat this organelle, there are different therapies, such as intelligent drug delivery systems or the modification of traditional treatments. At present, mitochondrial-directed photothermal therapy (PTT), photodynamic therapy (PDT), and chemodynamical therapy (CDT), have attracted worldwide attention due to their advantages, such as wide the-

rapeutic range, minimal toxicity, and excellent profile. non-invasive safety and low resistance (63–66).

On the other hand, deregulation of the ubiquitin-proteasome pathway is known to be associated with various diseases, particularly neoplastic ones; it is also related to late relapses, suggesting the development of acquired resistance. The use of proteasome inhibitors (PIs) is a therapy that has received attention from the pharmaceutical industry. Different classes and several inhibitors have been developed; however, only three were approved by the FDA and the EMA: bortezomib, carfilzomib, and ixazomib (67).

Regarding RNA therapies, the miR-200 family are tumor suppressors and are commonly decreased in cancer. The miR-200 family has been reported as a valuable diagnostic and prognostic marker. (47). Therefore, these miRNAs can be packaged into vesicles for cancer therapy and chemoresistance.

Conclusions

The emergence of drug resistance is a barrier to effective cancer treatment. Resistance develops during chemotherapy, radiotherapy, molecularly targeted therapy, and immunotherapy in most cancer patients and decreases survival. Despite the enormous amount of information about

resistance, we are still far from finding a solution to the problem since chemoresistance is a multifactorial phenomenon involving the interaction of multiple genes and proteins between them. For this reason, it is necessary to have a detailed understanding of chemoresistance and the mechanisms that develop it.

It is necessary to acquire new approaches related to cancer treatments, which must consider the resistence of chemopharmaceuticals not as a possibility of occurrence but as a fact of appearance at any stage of therapy. Therefore, it is extremely important to study the genes involved in drug resistance in cancer, as well as their coding proteins, with a focus of make more efficient and less harmful therapies and achieve more patients and longer survival.

Conflict of interest and financing

The Authors have no conflict of interest.

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