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General Mechanisms of Resistance to Pharmacological Therapy Applied to Tumor Cells

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Abstract: The management of cancer involves procedures, which include surgery, radiotherapy and chemotherapy, whose are aimed at destroying tumor cells and preserving healthy tissues. Development of drug resistance is one of problems during the treatment of local and/or disseminated disease, also is one of the biggest problems in relapses of cancer. A plethora of cytotoxic drugs that selectively, but not exclusively, target actively proliferating cells include such diverse groups as DNA alkylating agents, antimetabolites, intercalating agents and mitotic inhibitors. Resistance constitutes a lack of response to drug-induced tumor growth inhibition. This article discusses the various mechanisms of acquired drug resistance that have been reported in the context of cancer drug therapies. The drug resistance may be inherent in a subpopulation of heterogeneous cancer cells or be acquired as a cellular response to drug exposure. Also, different mechanisms have been proposed that could explain tumor refractoriness due to resistance to anti-tumor drugs, some of them are: intrinsic resistance due to their genetic characteristics, acquisition of resistance mechanisms after exposure to a drug, mechanisms that alter transport of the drug. drug through the plasma membrane, DNA repair, alterations in target molecules, difficulty of the drug to access the target cells and growth factors. The knowledge of these mechanisms of resistance, could serve as a therapeutic strategy to control or delay the progression of the disease and therefore improve the quality of life of the patient.

Keywords: Cancer, Chemotherapy, Pharmacological Resistance, Tumor Cell

1. Introduction

The goal of all cancer treatment is the eradication of tumor cells while preserving or inflicting minimal damage to normal tissues. This is achieved in several ways, either by directly or indirectly inhibiting the signals necessary for the proliferation and viability of the tumor cells or by stimulating an immune response. Molecularly targeted therapies have shown promise in the management of patients with advanced cancers, often resulting in dramatic tumor responses and extending lives. However, such therapies are rarely curative and, in most cases, resistance emerges relatively rapidly. Drug resistance continues to be one of the biggest problems in the treatment of neoplasms, since in the end, most patients will die due to the progression of their disease, as this is refractory to the treatments administered [1].

The mechanisms that can explain the refractoriness of neoplastic diseases to treatments are several. Currently, in drug resistance (MDR), different cellular mechanisms have been identified that, individually or in combination, confer resistance in individual cells as well as in specific populations [2]. Among these mechanisms, the most prominent are shown in Table 1. Taken together, these observations highlight a pressing need to further elucidate the various mechanisms that drive disease progression during drug treatment as a key step towards developing therapeutic strategies to prevent or overcome such drug resistance in individual patients, according to the specific molecular characteristics of their tumor. Therefore, this article discusses the various mechanisms of acquired drug resistance that have been reported in the context of cancer drug therapies.

2. Methods

For the preparation of this work, a general bibliographic

search and review of articles related to the pharmacological treatment of cancer and the resistance of these drugs was carried out in order to know the current reality of the general mechanisms of resistance to pharmacological therapy applied to tumor cells. The articles were included in the review based on the relevance of their title, summary and content, original articles were used as well as review articles as well as the doctoral thesis of one of the authors of the article. Articles from the Pubmed portals were used, Scopus and EMBASE. For the realization of the revision, we need a number of 28 of important publications published from 1976 to 2016.

3. Cellular Transport Mechanisms and Drug Elimination

In the transport and elimination of drugs to the extracellular medium and in its nucleus-cytoplasmic redistribution, different transporting proteins actively participate. Usually, two large groups are distinguished: the adenosine tri-phosphate (ATP) -dependent transport proteins and other proteins whose function does not depend on ATP [2].

3.1. ATP-Dependent Transport Proteins

One of the mechanisms responsible for resistance to multiple hydrophobic cytotoxic agents and derivatives of natural products results in part from the expression of proteins capable of transporting substances through the cytoplasmic membrane against a concentration gradient, decreasing the intracellular amount of drug [3]. To perform this function as a reflux pump, said proteins require the hydrolysis of ATP, belonging to the superfamily of transplants ABC (ATP-binding cassette) since each of its members contains an ATP-binding zone [3]. These proteins show an important degree of structural homology and share part of their sequence, including the cytoplasmic regions where the domains capable of binding ATP are located [2, 4]. Up to now, 48 human genes have been identified that codify the different proteins of this superfamily, grouped in 7 different subfamilies (ABCA to ABCG) depending on their homology and the organization of their dominions.

They are, probably, the most frequent set of resistance mechanisms observed in tumors. Of this protein superfamily, the P-Gliocoprotein or type 1 drug resistance protein (gp-P or MDR1) stands out, which is the product of the expression of the MDR-1 gene located in the q21 region of human chromosome 7 [5] and It was in 1976, when P-gp was described that was associated with decreased drug permeability in Chinese hamster ovary cells [6]. Subsequently, it was demonstrated that said protein existed in normal cells and conferred multidrug resistance to human cells [7, 8]. It was shown that the P-gp was an energy-dependent flow pump [9].

The P-gp protein is one of the 48 ATP-Binding Cassette transporters (ABC transporters) [10]. ABC transporters facilitate the transport of several substrates through intra and extracellular membranes. All ABC transporters are capable of transporting cytotoxic drugs in the same way as P-gp. The clinical relevance of this fact is based on the fact that the in vitro studies prove that the cells that express these transporters effluence the cytotoxics and confers them resistance to drugs in cultures and the patients that present expression of ABC transporters in their cancer cells have an unfavorable prognosis. such as those of acute myeloblastic leukemia (AML) [11]. The gp-P acts on a wide range of substrates, including many anti-neoplastic drugs such as tubulin polymerising drugs (Colchicine), anthracyclines (Doxorubicin) or epipodophyllotoxins (Etoposide) [2, 12]. Knowing these P-gp acting processes as the main cause of multidrug resistance, could lead to their inhibition developing a new class of antineoplastic treatments effective against some types of cancer.

Another protein of interest within this superfamily is the resistance-associated protein MRP1 (multidrug resistance protein 1) which is located in the p13.1 region of human chromosome 16. MPR1 has the ability to transport and eliminate glutathione-conjugated drugs such as anthracyclines (Doxorubicin, Daunorubicin), Methotrexate and Vinca alkaloids (Vinblastine, Vincristine) [1].

Also within this family, another protein that was discovered in a line of resistant breast cancer is the Breast Cancer Resistance Protein (ABCG2) [13]. Their high levels in vivo and their function correlate refractoriness to the induction treatment and lower overall survival. [14-17].

3.2. Transport Proteins not Dependent on ATP

There are other cellular proteins capable of conferring resistance to drugs without the need to consume ATP. Special mention should be made of the protein associated with pulmonary resistance (LRP), identified in 1993 in the cell line of small cell lung carcinoma SW-1575 / 2R120. Considering its intracellular distribution, it is believed that LRP would be involved in the vesicular and nucleoplasmic transport of different antineoplastic drugs [18].

4. Mechanisms of Inactivation of Drugs Through Metabolic Pathways

There is evidence that the polymorphisms in enzymes involved in the metabolization of toxins can cause changes in the response to the treatment of haemopathies, or even in their development. Metabolic enzymes and detoxification enzymes that influence the pharmacological response are involved in this mechanism of resistance [19, 20].

This process can be divided into 3 steps. The first is mediated by cytochrome P450 (CYP450), which is a superfamily of enzymes that catalyze the oxidation of organic substances. The second step is the formation of conjugates between these organic substances and glutathione, glucuronic acid, or sulfate due to the enzymatic action of S-glutathione transferase (GST), UDP-glucuronosyl transferase, and sulfatase, respectively. These enzymes are expressed in all

tissues, but mainly in the liver. The third step of this detoxification process involves the export of substances metabolized by transmembrane pumps such as MDR1 and MRP1 [2].

5. Intracellular Signaling of Tyrosine Kinase Receptors

During cancer progression and during drug treatment, it is very common for cancer cells to undergo activation of different members of the superfamily of tyrosine kinase receptors (2). These receptors lead to the activation of the main survival routes such as PI3K / AKT, RAS / RAF / MEK / ERK and JAK / STAT, which gives cancer cells high resistance to drugs used for the treatment of neoplasms [21-23].

6. Pharmacological Resistance Mediated by the Cytoskeleton

The cytoskeleton is a dynamic structure that maintains cellular plasticity and is responsible for the structural changes that the cell undergoes in the processes of cell division and cell migration. That is why it is the object of a therapeutic target for many anticancer drugs. The pharmacological resistance developed by the microtubules of the cytoskeleton is produced through several mechanisms such as MDR1 and MPR1, alteration of the composition and structural organization of the microtubules and a poor signaling of the apoptosis mediated by p53, Bcl-2 and Bclx [24].

7. Pharmacological Resistance Mediated by Blocking the Signs of Death by Apoptosis

The goal of all chemotherapy drugs is the selective killing of cancer cells. The effectiveness of the treatment depends not only on the direct deterioration of the cells, but also on the ability to respond to these damages by inducing the apoptotic machinery. That is, the effect of drugs is associated with increased expression of "death genes" (SMAC / DIABLO, PTEN, p53) and decreased expression of "survival genes" such as IAPs (apoptosis inhibitory proteins), some members of the Bcl-2 family, the p53 protein and other proteins involved in the PI3K / AKT pathway [25]. Defects in the apoptotic machinery can be an alternative model of drug resistance. The pharmacological resistance in this context would be the result of the blocking of the activation signals of the apoptotic machinery, that is, an imbalance in the signaling of apoptosis where the resistance would produce an increase in the expression of "survival genes" and a decrease or inhibition of the expression of "death genes" [1].

8. Pharmacological Resistance Mediated by DNA Repair Mechanism

Another way in which cells can become resistant is through the action of DNA repair proteins [26]. The cells to survive must repair the damages caused to the DNA by the genotoxic drugs, but if the damage is very serious and the cell cannot be reversed it would go into apoptosis. However, in the tumor cells this physiological process can be inhibited through the action of the repairing enzymes of DNA damage, which would generate a mechanism of cell survival and resistance. Cleavage repair nucleotides [27] are one of the most important mechanisms involved in the repair of DNA damage, such as that induced by alkylating agents and platinum. There are 12 proteins involved in NR and overexpression of some of them would increase the cellular activity of DNA repair, inducing, therefore, pharmacological resistance [2, 28].

9. Conclusion

Resistance to tumor therapy is an unsolved problem in cancer treatment. A plethora of studies have attempted to explain this phenomenon and many mechanisms of resistance have been suggested over recent decades. This review various mechanisms of acquired drug resistance that have been reported in the context of cancer drug therapies, and providing the knowledge to understand the mechanisms of resistance, which allows focusing on them, and to achieve possible new therapeutic targets in resistant tumor cells.

Chemotherapy treatments are considered essential tools to combat the progression and spread of cancer to improve the quality of life and the survival of patients. Although most malignant tumors initially respond to chemotherapeutic treatments, after an unpredictable period, tumor cells develop mechanisms of resistance to treatment. At present, drug resistance continues to be one of the biggest problems in the treatment of neoplasms, since in the end, most patients will die due to the progression of their disease, as this is refractory to the treatments administered. Different cellular compartments are involved in the mechanism of drug resistance, and multiple mechanisms can be activated by individual cells at different times of cancer progression. The alteration of the pharmacological metabolism, the alteration of the signaling of the intracellular pathways, the crossed communication between different membrane receptors and the modification of the apoptotic signaling and the interference with the cellular replication are mechanisms that the cell uses to overcome the effect of the pharmacological compounds.

Although due to the large number of new drugs that are continually being established as novel treatments against cancer and the more than possible future resistance of tumor cells to these therapies, it is not possible for this article to be described all of them. However, we describe the mechanisms of resistance to pharmacological therapy developed to tumor cells, as opposed to the drugs more widely used and accepted

in the therapies against cancer disease. Therefore, we have described the mechanisms that can explain the refractoriness of neoplastic diseases, knowing them, allowing us to design new strategies in pharmacological therapy that aim to control, delay and even block the progression of the disease, which will directly influence survival and in a better quality of life of the patient.

Competing Interests

The authors declare that there is no competing interest.

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Author Contribution

DFL and CFL have made the conception and design, analysis and interpretation, drafting of the paper, critically reviewed and approved the definitive version submitted for publication.

References

[1] Fernández-Lázaro D. Análisis pre-clínico comparativo de la eficacia, mecanismo de acción y mecanismos de resistencia de dos fármacos inmunomoduladores (IMIDS), lenalidomida y pomalidomida, en mieloma múltiple. [Doctoral]. Salamanca: Salamanca; 2011.

[2] Fodale V, Pierobon M, Liotta L, Petricoin E. Mechanism of cell adaptation: when and how do cancer cells develop chemoresistance? Cancer J. 2011; 17(2):89-95.

[3] Dean M, Rzhetsky A, Allikmets R. The human ATP-binding cassette (ABC) transporter superfamily. Genome Res. 2001; 11(7):1156-66.

[4] Krishna R, Mayer LD. Multidrug resistance (MDR) in cancer. Mechanisms, reversal using modulators of MDR and the role of MDR modulators in influencing the pharmacokinetics of anticancer drugs. Eur J Pharm Sci. 2000; 11(4):265-83.

[5] Wang XJ, Zhang DL, Fu C, Wei BZ, Li GJ. MiR-183 modulates multi-drug resistance in hepatocellular cancer (HCC) cells via miR-183-IDH2/SOCS6-HIF-1alpha feedback loop. Eur Rev Med Pharmacol Sci. 2016; 20(10):2020-7.

[6] Juliano RL, Ling V. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. Biochim Biophys Acta. 1976; 455(1):152-62.

[7] Matsuoka S, Ballif BA, Smogorzewska A, McDonald ER, 3rd, Hurov KE, Luo J, et al. ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. Science. 2007; 316(5828):1160-6.

[8] Kartner N, Riordan JR, Ling V. Cell surface P-glycoprotein associated with multidrug resistance in mammalian cell lines. Science (New York, NY. 1983; 221(4617):1285-8.

[9] Chen CJ, Chin JE, Ueda K, Clark DP, Pastan I, Gottesman MM, et al. Internal duplication and homology with bacterial transport proteins in the mdr1 (P-glycoprotein) gene from multidrug-resistant human cells. Cell. 1986; 47(3):381-9.

[10] Szakacs G, Annereau JP, Lababidi S, Shankavaram U, Arciello A, Bussey KJ, et al. Predicting drug sensitivity and resistance: profiling ABC transporter genes in cancer cells. Cancer cell. 2004; 6(2):129-37.

[11] Marie JP, Zittoun R, Sikic BI. Multidrug resistance (mdr1) gene expression in adult acute leukemias: correlations with treatment outcome and in vitro drug sensitivity. Blood. 1991; 78(3):586-92.

[12] Fischer S, Pietsch M, Schirmer K, Luckenbach T. Identification of multi-drug resistance associated proteins MRP1 (ABCC1) and MRP3 (ABCC3) from rainbow trout (Oncorhynchus mykiss). Mar Environ Res. 2010; 69 Suppl:S7-S10.

[13] Ross DD, Yang W, Abruzzo LV, Dalton WS, Schneider E, Lage H, et al. Atypical multidrug resistance: breast cancer resistance protein messenger RNA expression in mitoxantrone-selected cell lines. Journal of the National Cancer Institute. 1999; 91(5):429-33.

[14] Benderra Z, Faussat AM, Sayada L, Perrot JY, Chaoui D, Marie JP, et al. Breast cancer resistance protein and P-glycoprotein in 149 adult acute myeloid leukemias. Clin Cancer Res. 2004; 10(23):7896-902.

[15] Steinbach D, Sell W, Voigt A, Hermann J, Zintl F, Sauerbrey A. BCRP gene expression is associated with a poor response to remission induction therapy in childhood acute myeloid leukemia. Leukemia. 2002; 16(8):1443-7.

[16] Damiani D, Tiribelli M, Calistri E, Geromin A, Chiarvesio A, Michelutti A, et al. The prognostic value of P-glycoprotein (ABCB) and breast cancer resistance protein (ABCG2) in adults with de novo acute myeloid leukemia with normal karyotype. Haematologica. 2006;91(6):825-8.

[17] Benderra Z, Faussat AM, Sayada L, Perrot JY, Tang R, Chaoui D, et al. MRP3, BCRP, and P-glycoprotein activities are prognostic factors in adult acute myeloid leukemia. Clin Cancer Res. 2005; 11(21):7764-72.

[18] Sánchez-Suárez P, Benítez-Bribiesca L. Procesos biomoleculares de la Resistencia a drogas. Cancerolgía 2006; 1:18-199.

[19] Ansari M, Krajinovic M. Pharmacogenomics of acute leukemia. Pharmacogenomics. 2007; 8(7):817-34.

[20] Bolufer P, Collado M, Barragan E, Cervera J, Calasanz MJ, Colomer D, et al. The potential effect of gender in combination with common genetic polymorphisms of drug-metabolizing enzymes on the risk of developing acute leukemia. Haematologica. 2007; 92(3):308-14.

[21] McCubrey JA, Abrams SL, Ligresti G, Misaghian N, Wong EW, Steelman LS, et al. Involvement of p53 and Raf/MEK/ERK pathways in hematopoietic drug resistance. Leukemia. 2008; 22(11):2080-90.

[22] McCubrey JA, Steelman LS, Abrams SL, Lee JT, Chang F, Bertrand FE, et al. Roles of the RAF/MEK/ERK and PI3K/PTEN/AKT pathways in malignant transformation and drug resistance. Adv Enzyme Regul. 2006; 46:249-79.

[23] Steelman LS, Abrams SL, Whelan J, Bertrand FE, Ludwig DE, Basecke J, et al. Contributions of the Raf/MEK/ERK, PI3K/PTEN/Akt/mTOR and Jak/STAT pathways to leukemia. Leukemia. 2008; 22(4):686-707.

[24] Galmarini CM, Kamath K, Vanier-Viornery A, Hervieu V, Peiller E, Falette N, et al. Drug resistance associated with loss of p53 involves extensive alterations in microtubule composition and dynamics. Br J Cancer. 2003; 88(11):1793-9.

[25] Chaudhry P, Asselin E. Resistance to chemotherapy and hormone therapy in endometrial cancer. Endocr Relat Cancer. 2009; 16(2):363-80.

[26] Das-Gupta EP, Seedhouse CH, Russell NH. DNA repair mechanisms and acute myeloblastic leukemia. Hematological oncology. 2000; 18(3):99-110.

[27] Henriquez OC, Baez SM, Von Oetinger A, Canas JR, Ramirez CR. Autonomic control of heart rate after exercise in trained wrestlers. Biol Sport. 2013; 30(2):111-5.

[28] Furuta T, Ueda T, Aune G, Sarasin A, Kraemer KH, Pommier Y. Transcription-coupled nucleotide excision repair as a determinant of cisplatin sensitivity of human cells. Cancer Res. 2002; 62(17):4899-902.