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Chemotherapy and Mechanisms of Resistance in Breast Cancer

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1. Introduction

1.1 Adjuvant

In the mid 1950s, we started to have a much better understanding of the biological mechanisms of establishment of metastases and the role of regional lymph nodes as an effective barrier to tumor spread, because malignant cells have been observed in the bloodstream (Fisher, Turnbull, 1955).

Early studies with adjuvant chemotherapy after surgery in solid tumors (breast adenocarcinoma implanted in mice) began in 1957 (Shapiro, Fugman, 1957). Based on these findings, Bernard Fisher and colleagues began in 1958, the first collaborative study with the objective of evaluating the response to systemic administration of perioperative chemotherapy in patients with operable breast cancer (Fisher et al, 1958). Good results were obtained in relation to disease-free interval and overall survival in premenopausal women (Fisher et al, 1968). Similar results were also observed by other authors, with the use of multidrug therapy (cyclophosphamide, methotrexate and fluorouracil (CMF) with or without prednisone) in advanced breast cancer (BC)(Canellos et al, 1974 and 1976, Bonadonna et al, 1976). Therefore, the addition of adjuvant polychemotherapy in BC showed gain by controlling survival of micrometastases in patients with lymph nodes affected by cancer or not (Fisher et al, 1975; Bonadonna et al, 1976; Early Breast Cancer Trialists Collaborative Group (EBCTCG), 1988; Bonadonna, Valagussa, 1983,1985,1987, Henderson, 1987, Fisher et al, 1989; Bonadonna et al, 1995; Mansour et al, 1998, Carlson et al, 2000 and NIH 2000).

1.2 Neoadjuvant therapy

Neoadjuvant chemotherapy is defined as a treatment option where chemotherapy is introduced before local treatment, either surgery or radiotherapy (Bear, 1998). This was introduced by De Lena et al (1978) who administered adriablastin and vincristine in 110 women with advanced BC, achieving response rates of 70% partial.

The biological rationale for using neoadjuvant chemotherapy was based on observations in animal models where the removal of primary tumor growth accelerated due to changes in metastatic tumor kinetics, suggesting that growth factors derived from tumor influence the

development of micrometastases. The prior addition of chemotherapy such as cyclophosphamide in mice transplanted with murine mammary tumor cells showed a significant reduction in the proliferation rate of residual tumor and metastases, and prolonged their survival (Gunduz et al, 1979, Fisher et al, 1989b; Fisher et al, 1989c).

The use of neoadjuvant chemotherapy has additional advantages in patients with locally advanced carcinoma, enhancing the possibility of performing conservative surgery due to the reduction of tumor size, as well as providing evidence in vivo of sensitivity to therapy and providing early treatment of micrometastases (Bonadonna et al. 1990; Wolff, Davidson, 2000, Kafka et al 2003, Hutcheon, Heys, 2004).

Studies demonstrated a significant increase in survival in patients with stage III breast carcinoma, influenced by neoadjuvant chemotherapy associated with local therapy (Canellos, 1976; Jacquillat et al, 1987 Valagussa et al, 1990). Six randomized trials compared the use of adjuvant and neoadjuvant therapy with the aim of measuring the survival of patients with complete clinical response rates from 6.6 to 41% and pathological complete rates of 3 to 29%, with high rates of breast conservation in patients undergoing neoadjuvant chemotherapy (Mauriac et al, 1991; Semiglazov et al, 1994; Scholl, 1994; Powles et al, 1995, van der Hage et al, 2001; Wolmark et al, 2001). One of the major studies related to neoadjuvant chemotherapy was the National Surgical Adjuvant Breast and Bowel Project B18 (NSABP B18), which showed no significant difference between the rates of disease-free survival and survival free of distant disease (among those who received neoadjuvant chemotherapy and those who received postoperative adjuvant chemotherapy). However, neoadjuvant chemotherapy allowed higher rates of conservative surgery and the study in vivo of tumor biology (Fisher et al, 1998). Further analysis, with a follow up of nine years, showed that patients under 49 years experienced a significant advantage in terms of survival rates and disease-free survival when they were submitted to primary chemotherapy in relation to patients 50 years or more, suggesting that age could influence the indication of neoadjuvant chemotherapy, continuing the strong correlation between the clinical primary tumor response to chemotherapy and prognosis (Wolmark et al, 2001).

The neoadjuvant therapy was extended for the treatment of patients with operable breast tumors initially with different chemotherapy regimens and variable rates of clinical response (Scholl et al, 1994; Ragaz et al, 1997, Fisher et al, 1997, Fisher et al, 1998). The clinical response to neoadjuvant administration of chemotherapy, namely the reduction of tumor size, was 10 to 75% in several studies (Kafka et al, 2003).

1.3 Mechanisms of resistance to chemotherapeutic agents

The main reasons responsible for treatment failure in cancer patients are the mechanisms of drug resistance and emergence of disseminated disease (Terek et al, 2003). We identified two types of resistance most relevant to BC: primary resistance, which corresponds to the clinical situation where the patient showed no response to therapy, and secondary or acquired resistance in which, initially, there is an observed response and a subsequent failure of the treatment regimen (Kroger et al, 1999).

Several mechanisms may cause the phenotype of multidrug resistance to chemotherapy drugs and are well characterized in in vitro experiments, including alterations in systemic pharmacology (pharmacokinetics and metabolism), extracellular mechanisms (tumor environment, multicellular drug resistance), and cellular mechanisms (cellular

pharmacology, activation and inactivation of drugs, modification of specific targets and regulatory pathways of apoptosis) (Leonessa et al, 2003, Riddick et al, 2005). Identification of factors that affect cell metabolism, which are related to drug resistance, will enable the identification of which patients are at particular risk of treatment failure.

Among the biochemical and molecular mechanisms of drug resistance, we stress: changes in the activity of topoisomerase II, alterations in the DNA repair mechanism, overexpression of P-glycoprotein; high intracellular concentrations of enzymes purification of cellular metabolism - among them enzymes the family of glutathione S-transferases (GSTs) and changes in the mechanisms of signaling via c-Jun N-terminal kinase 1 (JNK1) -and "apoptosis signal-regulating kinase (ASK1) required for activation of the" mitogen-activated protein (MAP kinases) in apoptosis and cellular restoration. These pathways are also mediated by proteins encoded by genes of GSTs (O'Brien, Tew, 1996; Burg, Mulder, 2002, L'Ecuyer et al, 2004).

Different response rates to particular chemotherapy regimens, as observed in patient groups with the same biological characteristics and stage, suggest the existence of different mechanisms of drug resistance, probably induced by genetic alterations (Hayes, Pulford, 1995; O'Brien , Tew, 1996; Pakunlu et al, 2003).

Among the mechanisms of purification of cellular metabolism involved in the inactivation of toxic substances to the cell there is the action of the enzyme family of GSTs in phase II metabolism of cell purification. The first evidence of their involvement in resistance to drugs used in chemotherapy have emerged from research published by scientific groups Schisswelbauer et al (1990), Tew (1994) and Hayes, Pulford, (1995). However, the relationship between GSTs and resistance to chemotherapy remains inconsistent (Riddick et al, 2005). This mechanism of resistance is related to the ability to regulate the action of enzymes involved in catalyzing electrophilic compounds harmful to cells from activation by cytochrome P-450 1A1 and 1B1 (Phase I). These compounds in turn are substrates for phase II enzyme systems, represented here by the family of GSTs, which are involved on two fronts in the process of drug resistance: production of protective enzymes of metabolism and cellular apoptotic processes via inhibition of JNK1 and ASK1 (Townsed, Cowan, 1989, Hamada et al, 1994; Tew, 1994; O'Brien, Tew, 1996; Gaudiano et al, 2000, O'Brien et al, 2000; Tashiro et al, 2001; Harbottle et al, 2001; Townsend, Tew, 2003b).

1.3.1 Glutathione S-transferases (GSTs)

The family of GSTs consists of eight classes termed cytosolic and symbolized by the Greek alphabet: Alpha, Kappa, Mu, Omega, Pi, Sigma, Theta and Zeta. They are highly polymorphic, with about 30% homology between their base sequences. Each of these classes has several alleles that reach 50% similarity between their base sequences, and are able to produce enzymes of phase II cell purification.

Cellular purification occurs through the ability to regulate the action of protein kinases involved in the catalysis of electrophilic compounds harmful to cells (xenobiotics) from the activation by cytochrome P-450 1A1 and 1B1, such as genotoxic chemical carcinogens and cytotoxic agents chemotherapeutic drugs and their metabolites by means of connection to glutathione (Fig. 1) (Townsed, Cowan, 1989, Shea et al, 1990; Tew, 1994, Shimada et al, 1996; Townsend, Tew, 2003a, b; Daly, 2003). The enzymes of the GST family represents about 5 to 10% of all cellular proteins (Burg, Mulder, 2002).

Studies have shown that the GST enzyme complex participates in the JNK1 and ASK1 pathways necessary for activation of MAP kinase signaling processes involved in apoptosis

and cellular restoration. They also participate in and catalyze the conjugation of electrophilic compounds and free radicals to the tri-peptide glutathione (γ-glu-cys-gly, or GSH), produced by GSH-reductase. Thus, they become less chemically reactive and more soluble, and its excretion facilitated by membrane enzyme complexes, among which stands out the GP1 enzyme encoded by the MRP1 gene family of ABC transporters (Arrick, Nathan, 1984; Townsed Cowan, 1989, Hamada et al, 1994; Tew, 1994; O'Brien, Tew, 1996, Morrow et al, 1998, Gaudiano et al, 2000; Harbottle et al, 2001; Burg, Mulder, 2002; Townsend, Tew, 2003a, b; Parl, 2005).

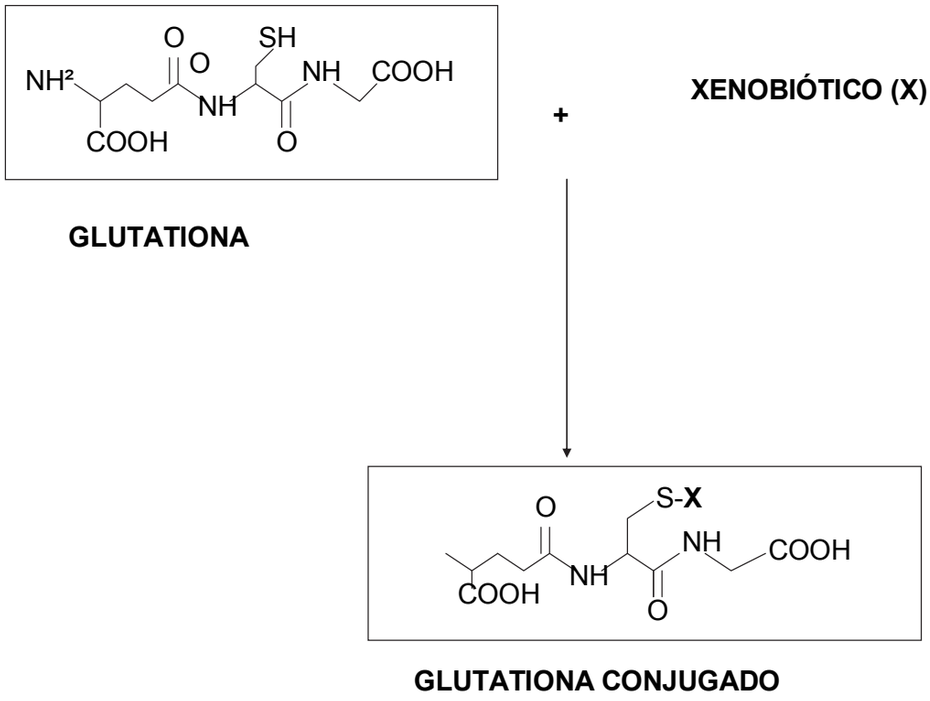


Fig. 1. Conjugation of glutathione to a generic xenobiotic (X) via catalysis by GSTs to form a conjugate of GST.

Glutathione (GSH) is a major intracellular non-protein substance present in the process of activation and inactivation of toxic substrates to the cell cycle. These reactions begins in the presence of free radicals and products released by the oxide-reactive phenomena of stress and inflammation than healthy and tumor cells are subjected (Arrick, Nathan, 1984; Russo, Mitchell, 1985, Asakura et al, 1999, Adler et al, 1999; Burg, Mulder, 2002; McIlwain et al, 2006). Thus, GSH plays an important role in cell survival and can be found in high concentrations in tumor tissue, where the highest enzyme activity of GSTs family exists (O'Brien, Tew, 1996, O'Brien et al, 2000).

GSH may present itself in several ways, most commonly its reduced sulfhydryl which is related to reactions with substances or reduced-oxide reactions with electrophilic substances. These reactions may be reversible or irreversible, spontaneous or mediated by

the enzymes of the family of GSTs (Arrick, Nathan, 1984; O'Brien, Tew, 1996; Burg, Mulder, 2002).

GSH has four functions in the anti-cancer therapy: cell protection by blockade of toxic substances to the cell, mediating the formation of toxic to cells, cellular targeting, allowing the efflux and influx of substances through association with enzyme systems membrane and therapeutic interaction through changes in the effectiveness of certain drugs (Arrick, Nathan, 1984). Among the substrates for the cytosolic enzymes of the family of GSTs are anti-neoplastic drugs such as melphalan, chlorambucil, adriamycin, cyclophosphamide, and platinum salts among others (Table 1), which, in the presence of these enzymes, have a lower intracellular concentration (Dirven, 1994; Paumi et al, 2001; Townsend, Tew, 2003a, b).

Direct substrates of GSTs
Chlorambucil
Melphalan
Nitrogen mustard
Mustard Phosphoramide
Acrolein
Carmustine
Hidroxialquilantes
Ethacrynic acid
Steroids
Substances not characterized as direct substrates of GSTs
Antimetabolites *
Antitubulin drugs *
Inhibitors of topoisomerases I and II *
Bleomycin
Hepsulfan
Mitomycin C *
Adriamycin *
Cisplatin *
Carboplatin

* Requires activation of JNK for cytotoxicity
(Adapted from Townsend, Tew, 2003b)

Table 1. Nonsteroidal anti-neoplastic agents associated with increased levels of GST and cellular resistance.

Cytotoxic and carcinogenic substances from the environment such as tobacco, alcohol and red meat, which are possibly related tocarcinogenesis in various organs such as breast, bladder and colon are also substrates for the enzymes of the GST family of

1.3.1.1 The glutathione S-transferases (GSTs) and breast cancer

The classes of GSTs are related to the BC classes Alpha, Theta, and Pi Mu. In this review we approach the last three, as they are most frequently studied and their analysis has provided further information in relation to adjuvant chemotherapy and CM.

The proteins that belong to the Mu class are encoded by a group of genes located on chromosome 1 (GSTM 1-5). These genes are related to various diseases and susceptibility to

various forms of cancer (Townsend, Tew, 2003a). The GSTM1 gene (Genbank access number AY532926) is the most studied and has four different allelic forms (GSTM 1 * A, B 1 * 1 * 1 * 0 null and Ax2 that are related to a variety of malignancies, as lung, colorectal, oropharyngeal, bladder and breast cancers (Bell et al, 1993; Ambrosone et al, 1995; Saarikoski et al, 1998; Helzlsouer et al, 1998; Jourenkova-Mironova et al, 1999, Dunning et al, 1999; Ambrosone et al, 2001; Loktionov et al, 2001 and Sgambati et al, 2002; Townsend, Tew, 2003a). However, some authors failed to demonstrate such a relationship (Bailey et al, 1998; Lizard-Nacolia et al , 1999; Garcia-Close et al, 1999).

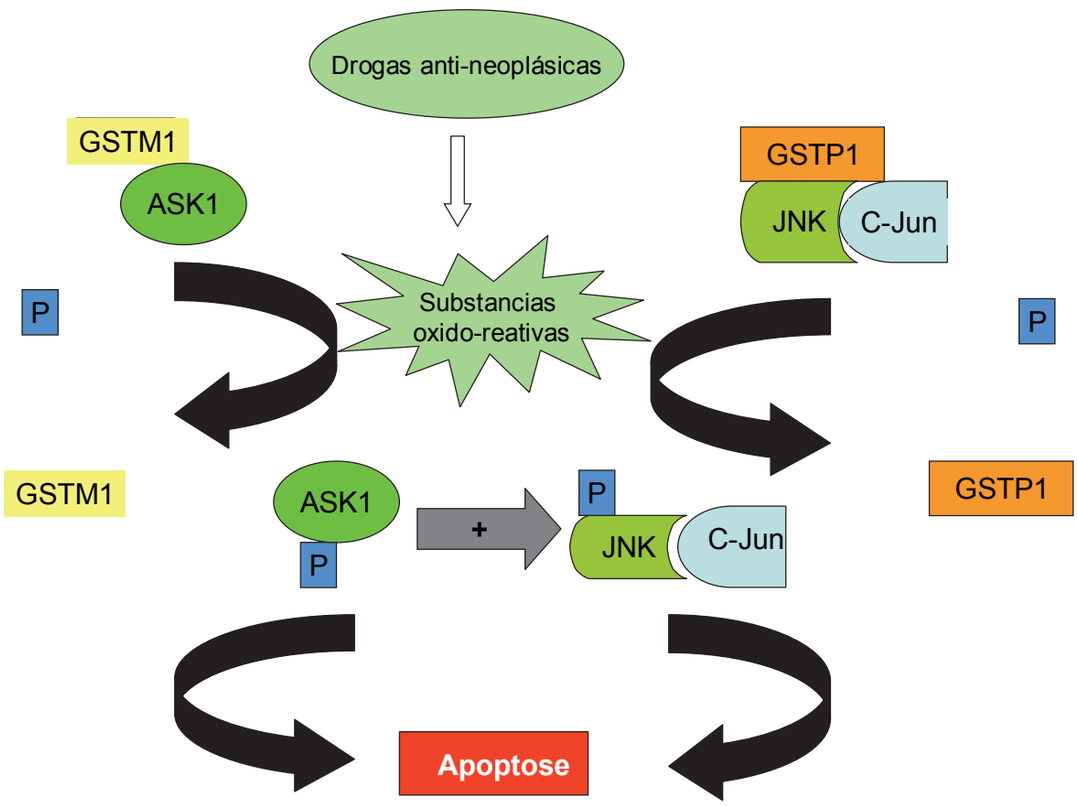
The enzymes encoded by the gene GSTM1 catalyze the conjugation of electrophilic compounds and free radicals by GSH and still exert an inhibitory effect on apoptosis via ASK1, independent of its catalytic action. This inhibition occurs while the enzyme complexes of GSTM1/ASK1 are related. In the presence of high concentrations of oxide-reactive substances, this complex dissociates, releasing enzymes to ASK1 phosphorylation and signaling of apoptosis (Fig. 2) (Cho et al, 2001).

The GSTM1 null genotype polymorphism results from the absence of the two alleles that determine gene expression. Thus, individuals with this genotype do not have the capacity to produce the enzymes necessary to catalyze the conjugation with GSH. Moreover, they also do not synthesize the proteins that coalesce to the ASK1 pathway proteins necessary for the inhibition of this pathway of apoptosis (Cho et al, 2001; McIlwain et al, 2006). The null genotype is present in 40 to 50% of the population (Tew, 1994), ranging from 22% in Nigeria, 58% among Chinese, 45% in Western Europe and up to 67% in Australia, and it is related to better response to some classes of chemotherapeutic agents against various types of cancer (Alpert et al, 1997; Ambrosone et al, 2001; Sgambati et al, 2002; Autrup et al, 2002; Townsend, Tew, 2003a; Khedhaier et al, 2003; Parl , 2005).

The proteins of the class Theta are encoded by two genes (T1 and T2), which are located on chromosome 22. The class GSTT1 (accession number AB057594 in Genbank) has three allelic forms: * The T1, T1 and T1 * B * 0 or null, but the latter is present between 10 and 30% in African populations, 10% in European and American populations, and 64% in Asian populations (Townsend, Tew, 2003a). The T1 null allele is associated with a predisposition to some cancers (Townsend, Tew, 2003a; Saarikoski, 1998; Helzlsouer et al, 1998; Jourenkova-Mironova et al, 1999 and Ambrosone et al, 2001), among them breast cancer in postmenopausal women, users of large quantities of alcoholic and longtime smokers, as well as in premenopausal women or nulliparous women who gave birth after age 30 (Park et al, 2000, Zheng et al, 2002, Zheng et al, 2003; Park et al, 2003), although some studies have not shown this relationship (Bailey et al, 1998; Garcia-Close et al, 1999; Millikan et al, 2000). The presence of the GSTT1 null form, in which there is not production of the enzymes, was associated with a better response to chemotherapy in patients with BC and the greater toxicity of some chemotherapeutic agents (Howells et al, 2001;Naoe et al, 2002; Khedhaier et al, 2003).

The class Pi, in turn, consists of only one protein encoded by a gene located on chromosome 11 and called GSTP1 (GenBank access number AY324387). The GSTP1 gene has three allelic forms. The wild GSTP1 * A (Ile105Ile/Ala113Ala) genotype results in the replacement of Ile by Val at least one amino acid at codon 105 and) and two polymorphic forms, GSTP1 * B (Val 105Ile Val/113 Val) where, in addition to the alteration observed in GSTP1B * there is also replacement of Ala by Val in at least one amino acid codon 113.))GSTP1 * C (105 Ile Ala. These forms are represented, respectively, in 68%, 26% and 7% of the Caucasian population (Townsend, Tew, 2003a).

The enzymes produced by gene GSTP1 * A prevails as a marker of carcinogenesis, since they are present in many tumor cells (Townsend, Tew, 2003a). Their relationship with cell protection is more related to performance in the apoptotic process. While the proteins encoded by the form "wild" GSTP1 * A are related to proteins of the JNK pathway, which inhibits apoptosis. This action will cease as the intensity of the phenomena of stress to which the cell is subjected to increase (fig 2), a phenomenon that occurs independently of its catalytic action. Since the polymorphic forms do not have the capacity to synthesize proteins that coalesce to JNK pathway enzymes and therefore do not have the ability to inhibit this pathway of apoptosis (Adler et al, 1999, Dang et al, 2005).



ASK1: "Apoptosis Signal-Regulating Kinase"
JNK / Cjun: "c-Jun N-terminal Kinase 1"
P: phosphorus atom

Fig. 2. Action of GSTM1 and GSTP1 on pathways of apoptosis. While related enzymes ASK1 and JNK1, the proteins encoded by the genes GSTM1 and GSTP1 exert an inhibitory effect of the corresponding pathways of apoptosis. Once exposed to substances oxide - reactive is the dissociation of the complex and phosphorylation of enzymes ASK1 and JNK1 pathways that pass the signal to the apoptosis pathway.

The involvement of enzymes encoded by the gene GSTP1 * A in cell survival processes by catalyzing GSH seems to be a secondary response or consequence of the phenomena of stress to which the cells are submitted and occur in two ways of acting. The first one is

mainly related to anthracycline chemotherapy drugs and their substrates when associated with the ABC membrane transporters, responsible for one of the mechanisms of complex cellular efflux of GSH / drug. The second route of action would be on inhibitory complexes GSH / drugs on the enzymes of class GSTP1 * A, stimulating the process of apoptosis (Nakagawa et al, 1988.1990; Tew, 1994; Helzlsouer et al, 1998, Adler et al , 1999, Sweeney et al, 2000; Tashiro et al, 2001, Wang et al, 2001; Autrup et al, 2002; Townsend, Tew, 2003a, Huang et al, 2003; McIlwain et al, 2006).

The presence and distribution of genes encoding the synthesis of enzymes of the family of GSTs in humans are variable. Some individuals do not express the genes GSTM1 and GSTT1, which determine the production of the enzyme purification. It is said that these people have "deleted" these alleles, known as GSTs null. These in turn are unable to promote catalysis of toxic substances with GSH and unable to promote inhibition of protein kinases required for the apoptotic process. Since the class Pi presents a substitution of amino acid isoleucine (Ile) by valine (Val) at codon 105 (GSTP1 * A → GSTP1 * B) This change, either in a strand of DNA (heterozygous) or both strands (homozygous) also makes cells unable to produce their own enzymes catalyzing GSH, which was similar to the GSTs null, and no longer inhibit the JNK apoptosis 1 (McIlwain et al, 2006).

Comparable studies have shown varying results on the correlation between GSTs and chemotherapy response in various fields of oncology, including CM. Some authors have found a positive relationship between the presence of these enzymes and increased chemotherapeutic resistance (Hamada et al, 1994; Dirven et al, 1994, Morrow et al, 1998, Sweeney et al, 2000, O'Brien et al, 2000; Harbottle et al, 2001; Allan et al, 2001; Ambrosone et al, 2001; Naoe et al, 2002, Dasgupta et al, 2003, Huang et al, 2003, Yang et al, 2005), while others failed to demonstrate such a relationship (Moscow et al, 1989; Leyland-Jones et al, 1991, Peters et al, 1993, Morrow et al, 1998, Alpert et al, 1997, Konishi et al, 1998; Osmak et al, 1998; Allan et al, 2001;Yang et al, 2005).

1.3.2 P-glycoprotein

The phenomenon of multi-drug resistance was first described in 1970 in ovarian cancer cells derived from Chinese hamsters exposed to increasing concentrations of various chemotherapeutic agents like actinomycin D, anthracyclines, vinca alkaloids and etoposide, until chemo resistant clones emerged (Bield, Riehm, 1970). Subsequently, Riordan and Ling (1979) showed the phenotype of multidrug resistance by measuring a deficit accumulation of cytotoxic drugs in the intracellular environment due to the action of a specific glycoprotein.

One of the proteins responsible for determining this resistance phenotype is the P-glycoprotein (Pgp), first described by Juliano and Ling (1976), responsible for the permeation and elimination of substances through the cell membrane (Carlsen et al, 1976; Riordan, Ling, 1979). This transmembrane protein has a molecular weight of 170 kd, 1280 amino acids, is encoded by the gene MDR-1 and depends on energy coming from the metabolism of adenosine triphosphate (ATP) (Sauna et al, 2001). The MDR -1 gene in humans is located on the long arm of chromosome 7 (7 q 21) consisting of a central promoter region and 29 exons ranging from 6.3 to 210 kilobases (Bodor et al, 2005).

Pgp is the most investigated of a superfamily called ATP - binding cassette transporters, or ABC multidrug transporters. It is encoded by some genes as MRP-1, MRP- 2, MRP-3, MRP-4, MRP- 5,MRP-6, MRP-8, BSPE, BCRP (Goldstein, 1996; Scotto, 2003) ABC transporters are characterized functionally by their ability to eliminate antiblastic hydrophilic drugs from the intracellular environment , as shown below (Fig.3), (Sauna et al, 2001).

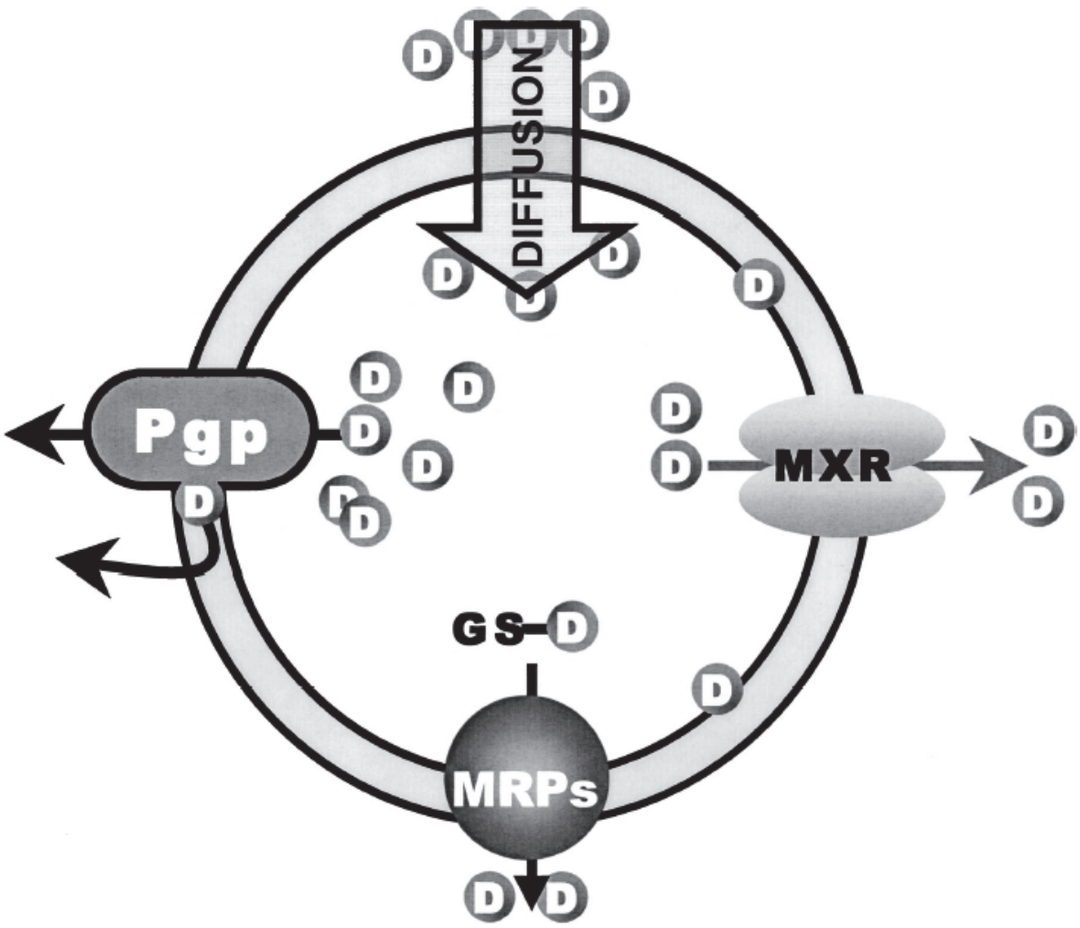


Fig. 3. Schematic representation of several proteins belonging to the superfamily multidrug ABC transporters, including Pgp. (Adapted from Sauna et al, 2001).

Several drugs are substrates to the protein encoded by MRP's as anthracyclines agents, vinca's alkaloid, taxanes, actinomycin D, among others (Goldstein, 1996). It consists of a basic structure composed of two transmembrane domains (TMD) associated with two helical domains attached to nucleotides, in a conical shape of 10 nm depth, oriented perpendicular to the cell membrane, as visualized in Fig. 4 (Leonessa, Clarke, 2003).
The three-dimensional shape of Pgp consists of a conical shape with a central pore, with its base open to the extracellular medium and its apex toward the intracellular region, virtually closed when this protein is not active (Leonessa, Clarke, 2003). The substrates of Pgp diffuse into the inner layers of the cell membrane along the propeller of their domains. With binding of the substrate on Pgp, ATP hydrolysis occurs after the conformational rearrangement of the protein obliterates the internal pore. Simultaneously, there is rotation of the helix, contributing to the decrease in the affinity between substrate and protein, eliminating it from the external environment. (Leonessa, Clarke, 2003). The mechanism by which Pgp interacts with this wide variety of substrates is still unclear. However, all substrates have in common that they are hydrophobic, have a molecular weight from 300 to 2000 Da; and some carry a positive charge at neutral pH (Sauna et al, 2001).

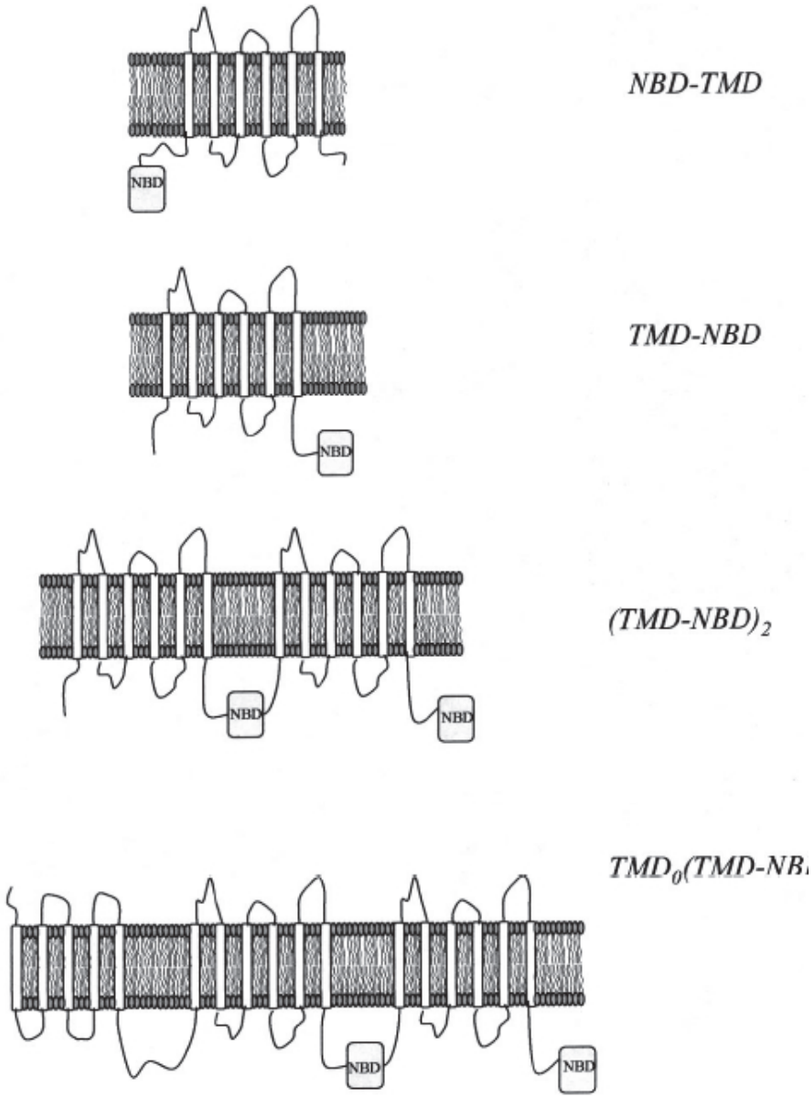


Fig. 4. Schematic representation of Tansmembranas domains (TMD) that make up the various ABC multidrug transporters, including Pgp. (Adapted from Leonessa, Clarke, 2003)

The expression of Pgp is not uniform across tissues, occurring both in normal and neoplastic tissues (Goldstein, 1996; Sauna et al, 2001) and is expressed physiologically in the blood-brain barrier, liver, kidneys, intestine, adrenal glands and testicles, functioning to control the absorption, distribution and excretion of xenobiotics (Gottesmann, Pastan, 1993; Ambudkar et al, 1999). High levels of Pgp are found in renal tumors, liver and colon, low concentrations are identified in bladder tumors, breast cancer and stomach cancer. In tumors that have failed initial treatment, its expression is particularly high, as in breast, ovarian and non-Hodgkin lymphoma (Goldstein, 1996). Tumors that initially show resistance to drug infusion (primary resistance) to anthracycline derivatives also express high concentrations of P-glycoprotein (Goldstein, 1996).

Pgp expression is and adverse prognostic factor on multivariate analysis, in patients with neuroblastoma and childhood sarcomas (Chan et al, 1990, Chan et al 1991), although this has

not been consistent association (Goldstein, 1996). The expression of Pgp associated with bcl-2 in acute lymphoblastic leukemia in adults is an independent prognostic factor for disease-free survival (Del Principe et al, 2003). In endometrial carcinoma, the immunohistochemical overexpression of Pgp is seen especially in premenopausal patients compared to patients of advanced age (Terek et al, 2003). In ovarian cancer, overexpression of MDR-1 gene is associated with decreased disease-free survival and tumor progression during chemotherapy (Kavallaris et al, 1996; Raspollini et al, 2005). In breast carcinoma, the expression of Pgp shows great heterogeneity due to the detection methods and different degrees of their induction by the use of multiple chemotherapeutic agents (Trock et al, 1997; Leonessa, Clarke, 2003). The expression of Pgp may be quantified by immunohistochemical analysis (IHC) or by use of polymerase chain reaction reverse transverse (RT-PCR) to identify the levels of ribonucleic acid type (mRNA) in order to identify its protein expression (Ro et al, 1990; Leonessa, Clarke, 2003). In patients with previously untreated breast carcinoma, the detection rates observed by IHC ranged from 0% (Yang et al, 1999) to 100% (Del Vecchio et al, 1997) with average rates of 45.9% (Leonessa, Clarke, 2003). We verified the expression of Pgp mRNA by RT-PCR ranging from 0 to 100% with average rates of 63% (Leonessa, Clarke, 2003). The comparison between the methods of evaluation shows sensitivity of detection comparable between the two methods, with agreement rates of about 73% between IHC and RT-PCR (Chevillard et al, 1996; Filipits et al, 1996).

1.3.2.1 Polymorphism C3435T of the MDR-1 gene

The single nucleotide polymorphism (SNP) is a substitution of bases, with sporadic occurrence in the population, which may or may not alter the function of the protein encoded by this codon (Hoffmeyer et al, 2000; Banhomme-Faivre et al, 2004). About 20 SNPs of the MDR-1 gene have been described by Hoffmeyer et al (2000) and Tanabe et al (2001). Brinkmann and Eichelbaum (2001) described 28 polymorphisms related to this gene, but the most studied polymorphism in these reports, with functional and clinical implications, is what happens C3435T in exon 26. In this SNP, the CC allele is considered as wild and replacing one or two of the nitrogen bases by T (CT or TT) represents the polymorphic genotype (Hoffmeyer et al 2000).

Hoffmeyer et al (2000), assessed by RT-PCR the distribution of this polymorphism in 21 healthy volunteers and showed that its occurrence was 23.9% homozygous and heterozygous, 48.3%. Cavaco et al (2003) reported that genotyping by using polymerase chain reaction linked to research the size polymorphism of restriction fragments (PCR-RFLP) in a sample of 100 healthy Caucasian Portuguese, demonstrated frequencies of 64.5% for the 3435T SNP and 35.5% for the C3435 SNP, resulting in the incidence in this population of the following genotypes: CC 12%, CT 47% and 41% TT. Balram et al. in 2003 described the incidence of the SNP C3435T using the methodology of PCR-RFLP in an Asian population comprised of 290 individuals (98 Chinese, 99 Malays and 93 Indians) and found that the CC genotype was present in 24% of Chinese, 25% of Malays, and 18% of Indians; the CT genotype was found in 44% of Chinese, Malays 46%, and 39% of Indians; the TT genotype was found in 32% of Chinese, 28% of Malays, and 43% of Indians. Hamdy et al (2003), using PCR-RFLP, described the following allele frequency distribution in 200 individuals of Egyptian origin: 34% genotype CC, 51.50% CT and 14.50%.

Experimental studies with cultured cell lines of breast and ovarian carcinomas subjected to the technique of RT-PCR showed that the basal expression of MDR-1 gene was absent or weakly present when associated with the TT genotype polymorphisms (Sauer et al,

2002). Hoffmeyer et al (2000) using the genotype represented by the SNP, determined the different forms of action of Pgp. These authors found, by sequencing the gene MDR-1 in 21 healthy volunteers, there was a significant correlation between the C3435T polymorphism in exon 26 and the function of Pgp where individuals with the TT genotype had lower protein function as compared to normal CC heterozygotes; and CT showed intermediate levels of Pgp function. This differential protein function resulted in different phenotypes associated with serum concentrations of several known substrates of Pgp, such as oral digoxin, These authors found a significant inverse correlation between the polymorphism of exon 26 and plasma levels of digoxin, which reflects its activity in vivo. Individuals with the TT genotype in the intestinal epithelium had significantly higher blood levels of digoxin than individuals with the CC and CT genotype, demonstrating functional differences in their activity and in their expression (Hoffmeyer et al, 2000). Other authors such as Kim et al (2001), confirmed these findings through research of this functional polymorphism using the technique of single-strand conformation polymorphism (SSCP) in peripheral blood samples of different populations of Euro-American individuals and African Americans. These authors, using another Pgp substrate, fexofenadine, reported that CC homozygotes had higher rates of serum concentration of this substrate when compared with the TT genotype, also demonstrating functional differences between different polymorphisms of the MDR-1 gene and consequently the expression of Pgp.

This scenario has clear implications when considering the therapeutic use of drugs that are substrates related to Pgp and may, depending on the functional action determined by this polymorphism, have different rates of clinical response. Kafka et al. (2003), showed a significant correlation between the C3435T polymorphism of the MDR-1 gene and partial and complete response to primary chemotherapy with anthracyclines, in patients with locally advanced breast carcinoma. These authors found that the presence of genotype TT was significantly correlated with clinical response, suggesting that the demonstration of this polymorphism could identify tumors sensitive and resistant to anthracyclines, and allow better individualization of therapy.

2. Summary

Different response rates suggest the existence of different mechanisms of drug resistance. Identification of factors which are related to drug resistance will enable the identification of which patients are at particular risk of treatment failure.

Pgp, encoded by the gene MDR-1, is the most investigated of a superfamily called ATP - binding cassette transporters, or ABC multidrug transporters. It has been involved as one of the drug-resistance's mechanisms since 1976. On the other hand, the action of GSTs family as cellular enzymes purification as signaling apoptosis has been studied since 1990's. The whole involvement of these enzymes is not totally clear yet, but seems that together represents a very important resistant mechanism to the chemotherapy treatments. More research is needed in this line of research to better understand these mechanisms.

3. References

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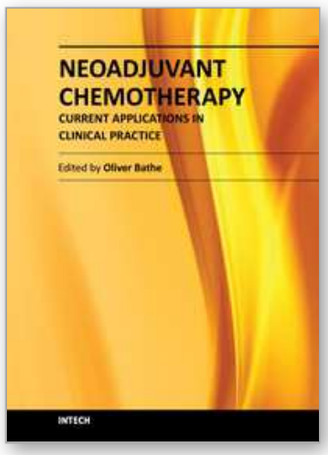

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The most significant advances in cancer therapy in recent years have involved the development of systemic therapeutics. With improvements in response rates in solid tumors, opportunities have arisen to enhance the effectiveness of surgery. Administration of systemic therapy prior to surgery - neoadjuvant chemotherapy - represents one approach by which clinicians have successfully reduced the extent of surgery and, in some instances, positively impacted on clinical outcomes. This collection of works by expert clinicians from a variety of disciplines represents an exploration of the current knowledge of the role of neoadjuvant chemotherapy in diverse tumor types.

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