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Review Article

P-glycoprotein Expression in Solid Tumors – An Analysis

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ABSTRACT

P-glycoprotein is an efflux transporter belonging to the ATP Binding Cassette (ABC) family of transporters and is encoded by *Multidrug resistance (MDR1)* gene. It is primarily involved in efflux of xenobiotics that permeate the external boundaries into the tissues. Chemotherapeutics are target oriented drugs for destruction of malgrowing cells to combat critical illness (viz., cancer, AIDS, malaria, tuberculosis, etc.) which are thus interpreted as harmful by the MDR system. This might cause overexpression of p-glycoprotein in such organs. Overexpression of p-glycoprotein rather than up-regulation of ABC-transporters are associated with resistance of tumours to multiple chemotherapeutic agents, thus reducing their bioavailability in the specific organs. The present review thus attempts to coalesce this expression data in solid tumors which maybe intrinsic to the organ or an after-effect of chemotherapy, thus altering the pharmacodynamics of drug permeation. For this purpose, peer reviewed publications have been analysed to delineate the range of fluctuation in p-glycoprotein expression in different organs after therapeutic intervention. It is extensively distributed and highly overexpressed in all neural tumors, reproductive and genito-urinary cancer, sarcomas, oral squamous cell carcinoma, NSCLC, hepatocellular carcinoma, cholangiocarcinoma, pancreatic tumor, *etc.* On the other hand, p-glycoprotein expression in cancer of the larynx, small cell lung carcinoma (SCLC), osteosarcoma, rhabdosarcoma, often show substantial decrease in expression, though not in all studies. There was no consistent increase or decrease in p-glycoprotein expression in all the tumors.

Key words: P-glycoprotein, Solid Tumors, Chemotherapy, Upregulation, Downregulation.

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INTRODUCTION

Tumor or malignancy afflicts all human organs of all ages, where hepatoblastoma and hepatocellular carcinoma are common in children. Solid tumors are non-haematopoietic in origin and may be differentiated into epithelial tumors and sarcomas which account for about 90% of the solid tumors. Children are also at risk for congenital tumors of the adrenal gland (neuroblastoma), kidney (Wilm's tumor), muscle (rhabdomyosarcoma) and retina (retinoblastoma).

Treatment of these include surgery, radiation and/or chemotherapy, where the last procedure involving system-wide drug administration, is most effective against metastatic tumours. However, multidrug resistance (MDR) impedes successful chemotherapy, which is primarily mediated via an efflux transporter p-glycoprotein, (encoded by ATP-binding cassette sub-family B member 1 (*ABCB1*) gene or *MDR1* gene). Structurally, it is a 170kDa transmembrane glycoprotein (N-terminal glycosylation), comprised of two ATP-binding sites in the cytoplasmic domain. It is physiologically distributed in organs functionally involved with the external environment viz., the intestinal epithelium, hepatocytes, renal proximal tubular cells and adrenal gland for expulsion of xenobiotics. Its expression in capillary endothelial cells of the blood-brain, blood-testis barrier and placenta indicate its relevance as 'gate-keeper', for conservation of the germ line and of the intrauterine embryo, thus preserving the internal *milieu*.[1-3]

This channel transports wide array of substrates ranging from drugs, chemotherapeutic agents, lipids, steroids, xenobiotics, peptides, bilirubin, cardiac glycosides, immunosuppressive agents, glucocorticoids, antiretroviral therapeutics, protease inhibitors and non-nucleoside reverse transcriptase inhibitors, with diverse molecular recognition adaptability.

In tumour cells, p-glycoprotein restricts intracellular drug concentrations, in the site of action. Its expression is upregulated in tumour cells transformed from tissues that express p-glycoprotein inherently (e.g., colon cancer) and in tumour cells transformed from tissues that do not normally express p-glycoprotein (e.g., breast cancer) after exposure to chemotherapeutic agents. As p-glycoprotein transports several chemotherapeutic agents, these tumours become resistant to the agent(s) administered and concurrently develop resistance to other chemotherapeutic agents that are p-glycoprotein substrates, resulting in MDR tumours. So, organ-based classification and inhibition of p-glycoprotein need research in anticipation of revival of sensitivity to chemotherapeutic agents.

There is a possible correlation between *MDR1* gene or p-glycoprotein expression levels and the quantity of applied chemotherapy in different tumours. In cell cultures, cell viabilities decrease significantly without increase of *MDR1* gene expression levels. Modulation of p-glycoprotein using chemosensitizers improves treatment efficacy in several types of tumour/cancer.

The present study aims to classify and analyze the *MDR1*/p-glycoprotein expression in different tumour specimens, with or without chemotherapy administration, based on data extracted from existing literature.

METHODOLOGY

About 255 online available peer-reviewed articles on p-glycoprotein / *MDR1* expression in solid tumors were initially studied by both the authors. The search was obtained by enlisting all solid tumors and tagging "p-glycoprotein, chemotherapy" individually from 1988 till date, with each of them through "Pubmed" or "Google" search engine.

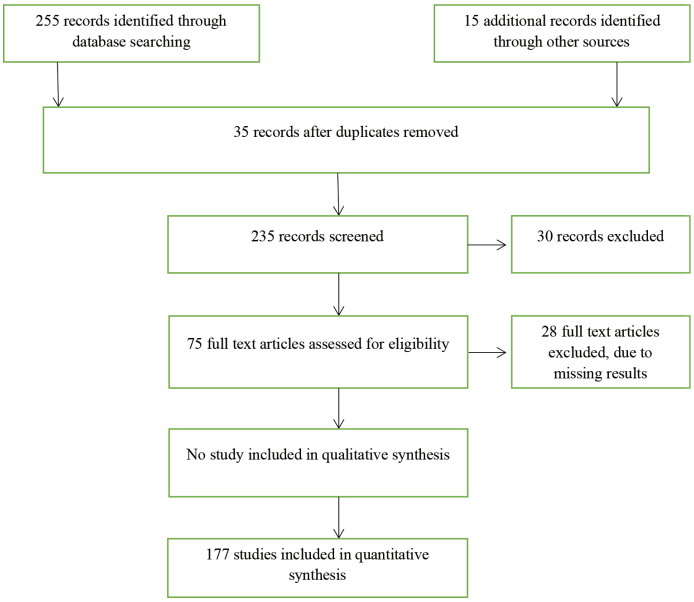

Figure 1: Flowchart of selection of relevant published articles.

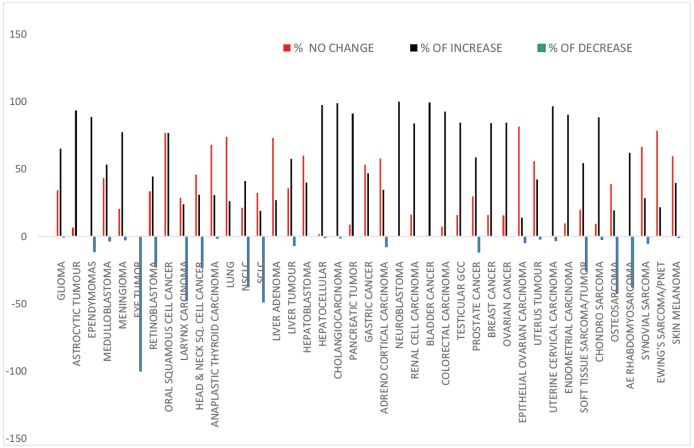

Figure 2: The percentage of increase / decrease / no alteration in the number of p-glycoprotein receptors in different solid tumors in response to chemotherapy.

Of these, only 177 publications with quantitative numerical data were included in the study. These were considered for tabulation and data analysis by converting the obtained data into percentage scale. Those with undefined or qualitative results had to be excluded (Figure 1).

RESULTS

Analysis of online data from 177 studies were classified into three categories in accordance with increased, decreased or sparse change of expression of *mdr1* gene/p-glycoprotein in the organ tumors after chemotherapy administration. Such variation in p-glycoprotein expression as a result of therapeutic intervention has been demonstrated graphically based on the percentage of numerical values accumulated from available literature (Figure 2). There was no consistent increase or decrease in p-glycoprotein expression in all tumors. It is extensively distributed and highly overexpressed in all neural tumors, reproductive or urogenital cancer, sarcomas, oral squamous cell carcinoma, non-small cell lung carcinoma (NSCLC), hepatocellular carcinoma, cholangiocarcinoma, pancreatic tumor, melanoma, *etc.* In most other forms of cancer viz., gastric carcinoma, cancers of the thyroid, soft tissues, peripheral primitive neuroectodermal tumours (PNET), osteosarcoma, medulloblastoma, etc., it is primarily overexpressed in response to chemotherapy. On the other hand, p-glycoprotein expression in cancer of the larynx, small cell lung carcinoma (SCLC), osteosarcoma, rhabdosarcoma, often show substantial decrease in expression, though not in all studies. The bar diagram in Figure 2 provides an approximate idea regarding the upregulation and downregulation of p-glycoprotein receptors or *MDR1* gene in response to chemotherapy. It diagram shows that some organs show increase in receptor quantity after chemotherapy, indicating decreased chemosensitivity, i.e., the response to the drugs probably decreases when the aforesaid organs are affected by cancer. Drugs for cancer, malaria, AIDS and tuberculosis are complicated and complex in nature and resemble xenobiotics to a certain extent. This compels our physiological system to recognize these valuable curative drugs as potent harmful agents. The p-glycoprotein receptor analyzes and extrudes these chemotherapeutic drugs out of the cell in which it resides, thus resisting the therapy.

DISCUSSION

Though the sample sets were non-uniform and the results were an outcome of admixture of both *in vitro* and *in vivo* observations, yet there are broad areas of commonality. Overexpression of either of the MDR genes, *MDR1* or Metal Resistance Protein (MRP), rather than up-regulation of ABC-transporters,[4] is associated with resistance of tumours to multiple chemotherapeutic agents. Downregulation of the receptors in response to a drug would imply chemosensitivity. There exist individualistic differences in chemotherapy sensitivity and expression of *MDR1*.[5,6] It is often inversely related to the level of p-glycoprotein expression in inoperable tumours or its expression may not be of aggressive phenotype and thus not influence survival.[7] Age, gender and physiological stage may all be contributory to the outcome. P-glycoprotein immunoreactivity was found to be less with advanced age in endometrial carcinoma but reverse in premenopausal patients.[8] Its expression was observed to be minimal in less-differentiated[9] and aggressive metastasis.[10] Higher *MDR1* expression in the invasive tumours compared with non-invasive tumours suggests that *MDR1* expression and invasiveness may be linked.[11]

Non-uniformity in expression of p-glycoprotein in different tumors maybe attributed to multiple factors beyond the organ per se. Irradiation,[12] radiotherapy,[13] hyperthermia mediated by activation of p38,[14] increased methylation,[15] may singly or synergistically be contributory towards overt expression of p-glycoprotein thus inducing drug resistance. This may also be the result of a mechanism involving stabilization of a diverse group of mRNAs.[16] The p-glycoprotein mRNA turnover rate is lower in tumours than in normal organs.[17] *MDR1* codon 3435 single nucleotide polymorphism at C/C genotype has been observed to be chemosensitive to platinum-based therapy than patients with C/T and T/T, without significant difference in overall survival.[18] This is irrespective of the organ involved in chemosensitivity.

Expression of survivin and p-glycoprotein may be related to malignant tumour progression.[19] There might be a correlation between loss of p53 function and expression of MDR.[20] p53[21] and p27[22] may be one of the active regulators of the *MDR1* transcript and chemoresistance.

To circumvent this, alternative approaches comprising of new cytotoxic agents, gene directed applications[23] through specifically directed adenoviral delivery of ribozymes[24] or hurling of nano-therapeutic particles inside the cell *per se* maybe attempted. Knockdown of *MDR1* significantly enhanced retention of the chemotherapeutics and decreased the efflux in *MDR1*-positive cells.[25] Modulation

of p-glycoprotein may be achieved by co-administration with chemosensitizer inhibitor or modulator along with the substrate[26-28] thus improving effectiveness of chemotherapy, especially in the highly differentiated tumours. Such simultaneous administration inhibits net intestinal absorption of therapeutics, altering their pharmacokinetics and therapeutic efficacy.[29] Among others, RNA interference,[30] transduction and expression of human TNF-alpha,[31] transfection of hIL-2 gene[32] can reverse expression of *MDR1* mRNA and p-glycoprotein in the drug resistant cell line. ERK1, 2 and JNK,[14] ROS acting as second messengers in tyrosine kinase signalling pathway may downregulate p-glycoprotein[33] which may again instigate drug-resistant quiescent cells in tumors for cell-cycle activity.[34]

Correlating the efflux transporter expression with chemosensitivity might be beneficial as an independent prognostic molecular marker[35] in the identification of individuals with multidrug resistance, to design alternately appropriate therapeutic modalities.[36] However, *MDR-1* mRNA is not a predictive of survival and metastatic progression does not coincide with MDR1 protein upregulation.[37]

CONCLUSION

The overall response of MDR1/p-glycoprotein suggests that in most tumours, chemoresistance far exceeds chemosensitivity, necessitating co-adminstration of nontoxic inhibitors, thus manipulating the drug efflux. The receptor expression is variable despite similarity in the type of tumour, indicating multifactorial regulation of the transporter. Quantitative studies on patients with complete follow-up for detailing expression of *MDR1* /p-glycoprotein and associated markers may help comprehend the contribution of these efflux pumps to the chemoresistance and address their predictive role. This will also help to formulate/administer drugs which shall circumvent p-glycoprotein mediated drug efflux.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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