

REVIEW ARTICLE

METABOLIC ENZYME CONSIDERATIONS IN CANCER THERAPY

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The clinical application of new antineoplastic drugs has been limited because of low therapeutic index and lack of efficacy in humans. Thus, improvement in efficacy of old and new anticancer drugs has been attempted by manipulating their pharmacokinetic properties. Four inter-related factors, which determine the pharmacokinetic behavior of a drug include absorption, distribution, metabolism and excretion. The drug-metabolizing enzymes have been classified in two major groups: phase I and phase II enzymes. Phase I enzymes comprise the oxidases, dehydrogenases, deaminases, hydrolases. Phase II enzymes include primarily UDP-glucuronosyltransferases (UGTs), glutathionetransferases (GSTs), sulfotransferases (SULTs), N-acetyl transferases (NATs), methyltransferases and amino acid transferases that conjugate products of phase I reactions and parent compounds with appropriate functional groups to generate more water soluble compounds which are more readily eliminated. The importance of these enzymes in the metabolism of specific drugs varies according to the chemical nature of the drug, Drug metabolism is modulated by factors that change among species and even among individuals in a population. Such factors can be environmental or genetic in origin, and influence how a drug is metabolized and to what extent. An awareness of these variables is invaluable when the safety and efficacy of new anticancer drugs are evaluated ¹

Key words : Cancer, metabolic enzyme consideration.

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Enzymes involved in the metabolism of anticancer drugs ; Phase I Metabolism

Oxidases

Cytochrome P450: Cytochrome P450s are generally considered to represent by far the most important system involved in drug metabolism. They are heme-containing enzymes with characteristic ferrous-carbon monoxide absorption maximum at near 450 nm. They are anchored to the smooth endoplasmic reticulum, and require molecular oxygen and coupling to a NADPH reductase. The most abundant human CYP450 family is CYP3A, which handles about 60% of the total drug oxidation reactions. CYP450 isozymes present genetic polymorphisms with different distributions across ethnic groups. The expression of several CYP450s may also be influenced by endogenous factors such

as growth hormone, glucocorticoids and estrogens and/or environmental factors such as nutritional state, exposure to toxicants, drugs and dietary constituents (2).

Flavin-containing Monooxygenases

Flavin-containing monooxygenases (FMOs) are microsomal enzymes that also depend on NADPH as cofactor. They are efficient at the oxidation of heteroatom-containing molecules such as primary and tertiary amines. Examples of their substrates are nicotine, cimetidine and tyramine. There are five families of FMOs identified in humans, FMO1, FMO2, FMO3, FMO4 and FMO5, which vary in functional activities and tissue expression. FMO3 is the major form in the liver, and is involved in the metabolism of biogenic amines and inactivation of xenobiotics (3).

Xanthine Oxidoreductases

Xanthine oxidase is a member of the molybdenum hydroxylase flavoprotein family. Xanthine dehydrogenase, a different form of the same gene product, and xanthine oxidase, are together referred to as xanthine oxidoreductases. In mammals, XORs are mainly responsible for the catabolism of purines, although they metabolize other endogenous and xenobiotic compounds. The XOR system has been found in many species. Major sites of expression in mammals are the liver and intestine, but relative to other species, humans express low levels of XOR. Increased tissue-specific expression of XOR has been reported in response to several cytokines and dexamethasone. Induction by ethacrynic acid, carbon tetrachloride and buthionine sulphoximine out of a panel of 21 compounds was recently reported. It is well established that XOR activity is decreased in several animal tumors, including hepatomas, colon and renal carcinomas, yet, results in humans have been contradictory because low levels of activity have made it difficult to identify patterns of XOR expression in human tumors. Anthracyclines such as doxorubicin, daunomycin and marcellomycin are reduced by xanthine oxidase to the corresponding semiquinone under aerobic conditions. Mitomycin C is reduced by xanthine oxidase under aerobic conditions to the semiquinone free radical with consequent formation of reactive oxygen species. Conversely, anaerobic conditions lead to the formation of 2,7-diaminomitosenone, a DNA alkylating metabolite. It is important to consider drug interactions when administering xanthine oxidase inhibitors. For example, inhibition of xanthine oxidase by allopurinol causes an increase in plasma levels of 6-mercaptopurine with possible toxic effects^{4,5}.

Reductases

NAD (P)H:Quinone Oxidoreductase 1

NQO1 is an obligate two-electron reductase involved in antioxidant defense; it uses either NADPH or NADH as cofactor and is inhibited by dicumarol. It is a cytosolic enzyme that functions as a homodimer containing one FAD per unit. NQO1 is present in tissues requiring protection from oxidative damage. NQO1 reduces quinones to hydroquinones in a single step, therefore bypassing the formation of the toxic semiquinone intermediates. Although this is considered a detoxification pathway, the resulting hydroquinones may in some cases form semiquinones, which in turn

generate reactive oxygen species. Anticancer agents have been designed to take advantage of NQO1 because this enzyme is expressed at high levels in many human solid tumors and the hypoxic environment present in solid tumors would favor reductive metabolism. A successful agent in this group of drugs called “bio-reductive alkylating agents” is mitomycin C a quinone-containing drug activated by NQO1 to reactive metabolites that cross link DNA^{6,7}.

Dehydrogenases

Aldehyde Dehydrogenase

Detoxification of aldehydes involves their oxidation to carboxylic acids by the NADP-dependent aldehyde dehydrogenases (ALDHs). Endogenous ALDH substrates include acetaldehyde, retinal and the other intermediates in the metabolism of biogenic amines, carbohydrates, lipids, aminoacids, vitamins and steroids. Aldehydes generated from metabolism of drugs and environmental agents are also substrates for these enzymes. The most important ALDHs are ALDH1A1 and ALDH3A1. These two enzymes are important in the detoxification of cyclophosphamide and other oxazaphosphorines. Their expression levels in tumors are inversely correlated with resistance to cyclophosphamide⁸.

Dihydropyrimidine Dehydrogenase

The initial and rate-limiting step for the catabolism of uracil and thymine is catalyzed by dihydropyrimidine dehydrogenase (DPD), an NADPH-dependent cytosolic enzyme. DPD is a dimer composed of two identical subunits with several tightly bound prosthetic groups, including two FMNs, two FADs and at least two [4Fe-S] clusters. Importance of DPD as a metabolic enzyme derives from the relevance of its substrate 5-fluorouracil (5FU). 5FU is a widely used agent for breast, head and neck, and colorectal cancers, its low bioavailability and high clearance, are primarily due to DPD catabolism⁹.

Enzymes involved in the metabolism anticancer drug : Phase II metabolism.

Glucuronosyl Transferases: The UDP-glucuronosyltransferases (UGTs) are microsomal enzymes that catalyze the conjugation of endogenous and exogenous substrates with UDP-glucuronic acid. Glucuronidation is in general seen as a detoxification process in which, lipophilic molecules are rendered hydrophilic for increased

transport into excretory organs and more efficient elimination in urine or bile. Some glucuronides show pharmacological activity such as morphine-6-glucuronide, and may be toxic glucuronides, such as acylglucuronides of non-steroidal anti-inflammatory drugs. Crigler-Najjar syndrome type II, a treatable disease, is characterized by small amounts of diglucuronides and monoglucuronides in duodenal biliary secretions. Gilbert's syndrome, is a mild condition that does not require treatment, yet, it has been linked to anticancer agent toxicity. Irinotecan, a potent inhibitor of topoisomerase I, is hydrolyzed to the active metabolite SN-38, which is eliminated primarily through glucuronide conjugation (10-11).

Sulfotransferases

The Sulfotransferases are cytosolic enzymes that catalyze the sulfation of both endo and xenobiotic compounds. They require phosphoadenosine phosphosulfate (PAPS) as sulfate donor. Two major families of sulfotransferases have been identified based on sequence homology and enzymatic properties. SULT1 enzymes transfer a sulfonate group to phenols and SULT2 enzymes to alcohols. Tamoxifen used in the treatment of breast cancer and as a prophylactic agent (12).

N-Acetyltransferases

The N-Acetyltransferases (NATs) require acetyl CoA as cofactor for their activity. There are two known forms: NAT1 and NAT2, with different substrate specificity. NAT1 specifically acetylates *p*-aminobenzoic acid and *p*-aminosalicylic acid while NAT2 is specific for isoniazid and sulfamethazine. Using specific riboprobes, Windmill *et al.* found that both isozymes are expressed in liver, gastrointestinal tract, ureter, bladder, and lung. Variation in the activity of these enzymes was one of the very first examples of genetic polymorphism in drug metabolizing enzymes. Patients administered isoniazid presented unexpected neurologic side effects as a result of drug accumulation due to slow acetylation of the drug (13).

Glutathione S-Transferase

The glutathione S-transferases (GSTs) have a primary role in the inactivation of electrophilic compounds by conjugation to glutathione. Compounds that are electrophiles such as epoxides, alpha-beta unsaturated ketones and halogenated hydrocarbons are substrates for GST. Endogenous substrates include prostaglandins, steroids and the

histidine metabolite urocaric acid. Glutathione conjugates can be excreted through the bile or the kidney. In the kidney, GSH conjugates are processed to mercapturic acid conjugates through the consecutive action of glutamyl transpeptidase, dipeptidase and cysteine conjugate lyase. GSTs are found in many tissues at different expression levels and under different regulatory mechanisms. The GSTP enzymes in particular, are expressed at high levels in proliferating cells and in human tumor cell lines. Considerable efforts have been devoted to identify specific inhibitors that could enhance the efficacy of alkylating agents such as thiopeta, a known substrate for hGSTP1-1. Haloenol lactone, a mechanism-based inhibitor of GSTP, was found to increase the toxicity of cisplatin in a human renal carcinoma cell line. In other example, ethacrynic acid, a substrate for GSTs and an irreversible inhibitor of GSTP, potentiated the cytotoxicity of chlorambucil in breast cancer cells resistant to nitrogen mustards (14-15)

***b*-Glucuronidase**

b-Glucuronidase presents exoglycosidase activity towards *O*-glucuronides. The bacterial enzyme, present in the intestinal flora, has been associated with the enterohepatic recirculation of drugs excreted in bile as glucuronide conjugates. A decrease in the toxicity of 1-nitropyrene in rats was observed after pretreatment with the *b*-glucuronidase inhibitor D-glucaro-1,4-lactone. In addition, enterohepatic recirculation and delayed intestinal toxicity of SN-38 observed in patients treated with irinotecan, has been attributed to deconjugation of SN-38 glucuronide by intestinal flora (16).

Arylsulfatase

There are three major families of arylsulfatases, the lysosomal enzymes arylsulfatases A and B that hydrolyze sulfated glycolipids and dermatan sulfate respectively, and arylsulfatase C, a microsomal enzyme that hydrolyzes sulfate conjugates of steroids and thyroid hormones (17).

Epoxide Hydrolases

The mammalian epoxide hydrolases are present in the cytosol and the endoplasmic reticulum. The major role of the microsomal enzyme is the inactivation of xenobiotic compounds by *trans*-addition of water to epoxides. Structure and catalytic activities of these enzymes have reviewed by Fretland *et al.*. Several anticancer agents, including the antiangiogenic drug TNP-470 and bropirimine

are metabolized to reactive epoxides or arene oxides by CYP450 and detoxified by the microsomal epoxide hydrolase (18).

Carboxylesterase

A variety of drugs containing ester or amide bonds are detoxified by the carboxylesterases. Several inducers of CYP450 also induce carboxylesterase and their co-administration with substrates should be carefully evaluated (19).

Metabolism of anti-cancer drugs

The drugs reviewed are classified based on their mechanism of action including: antimetabolites, DNA-binding drugs, inhibitors of chromatin function (topoisomerase and microtubule inhibitors), drugs affecting endocrine function and the new target-based drugs.

Antimetabolites

Antimetabolites act by inhibiting enzymes essential for the synthesis of RNA and DNA through bioactivation that takes advantage of differences in the metabolic capacity of cancers cells. Several reviews have been published on the metabolism of antimetabolites. Peters and coworkers (20) have shown the metabolism of folate antagonists/antifolates, pyrimidine antagonists, cytidine analogs, purine antagonists, and ribonucleotide reductase inhibitors. An important aspect of most antimetabolites is that they are prodrugs. For example, ara-C is converted into the 5'-triphosphate ara-CTP, which is the active form of the drug. Its inactivation involves deamination to 1- β -D-arabino-fluorano-syluracil (ara-U) catalyzed by cytidine/deoxycytidine deaminase. Aza-CdR is bioactivated by deoxycytidine kinase to aza-dCMP. Gemcitabine and ara-C, are bioactivated to the 5'-triphosphates and act through a variety of mechanisms that include incorporation into replicating DNA which inhibits DNA synthesis and cell growth. Cytotoxicity of gemcitabine correlates strongly with the extent of dFdCTP formation, incorporation into DNA and inhibition of DNA synthesis (21). 6-Mercaptopurine has an interesting bioinactivation mechanism. It is inactivated through S-methylation catalyzed by the enzyme thiopurine methyltransferase (TPMT). TPMT polymorphism is important in the metabolism of this drug.

A relatively new class of specific inhibitors of ribonucleotide reductase, the polyhydroxy-substituted benzohydroxamates, exhibited potent

anticancer activity. Among these compounds, 3,4-dihydroxybenzamidoxime significantly inhibited the growth of several tumor cell lines (22).

DNA-alkylating Drugs

Covalent DNA-binding drugs include nitrogen mustards, aziridines, alkane sulfonates, platinum complexes and oxazaphosphorines. Metabolism of older drugs including nitrogen mustards, 2-chloroethylnitrosoureas and alkane sulfonates has been reviewed by Lind and Ardiel (23).

Nitrogen Mustards

The nitrobenzamide nitrogen mustards are bioreductive drugs with a potential use as hypoxic cytotoxins or in directed enzyme prodrug therapy.

1. **CB 1954** had potent cytotoxic activity against the Walker rat adenocarcinoma cells. NQO1 reduces CB1954 to a hydroxylamine, which is subsequently converted to a bifunctional crosslinking agent by thioesters. The particular sensitivity of the Walker rat carcinoma cells was linked to expression of NQO1 (24).
2. **SN 23862** is a new nitrogen mustard analog of CB 1954. Similar to CB 1954, SN 23862 is extensively bioactivated by nitroreduction. Sequential oxidative dechloroethylation of the nitrogen mustard moiety yields the non-toxic half mustard and the 5-amine (25).

Aziridines

Metabolism of aziridines including thiotepa, altretamine (hexamethylmelamine), and mitomycin C was reviewed in detail by Graham *et al.* (26). Briefly, thiotepa is metabolized by CYP450 to tepepa, which has the same or even higher activity. **KW-2149** is a new mitomycin C analog with a similar broad spectrum but superior antitumor activity. Three metabolites detected in mouse plasma after intravenous administration of [³H]KW-2149 were tested for their cytotoxicity, a methyl sulfoxide (M16), a symmetrical sulfoxide dimer (M18) and an albumin conjugate. M18 is the active metabolite and was more efficient than KW-2149 at cross-linking DNA in two different *in vitro* assays. Interestingly, KW-2149 and M18 require activation by GSH while mitomycin C requires activation by NQO1. Thus, although the ultimate cytotoxic mechanism may be the same, pathways of bioactivation of these compounds appear different

(27).

Bleomycins

Bleomycins (BLMs) were extracted from cultures of *Streptomyces verticillus*. The common structure of BLMs is the bleomycinic acid, a glycopeptide with two sugars and five aminoacids, which contains a bithiazole moiety that confers intrinsic fluorescence to the molecule. BLM A and BLM B are the active contents of the antineoplastic drug Bleomoxane. The mechanism of antitumor activity seems to be partial intercalation into DNA. Tumor resistance to BLMs has been suggested to involve metabolic inactivation by BLM hydrolase. *Liblomycin (NK313)*, a promising analog already in clinical trials, has less pulmonary toxicity and similar antitumor potency. Unlike other BLMs, it acts by cleaving DNA(28). The antibiotic *Victomycin*, isolated from the actinomycete *Streptosporangium violaceochronogenes* belongs to the phleomycin-bleomycin group. Victomycin was active against sarcoma 180 and Ehrlich ascites carcinoma. Metabolism of BLMs is related to a specific but not fully characterized BLM-hydrolase. Two metabolites, deamino-BLM (A2) and deamido-BLM B2 were detected in incubations with cultures of isolated rat hepatocytes (29).

Inhibitors of Chromatin function

Topoisomerase Inhibitors

Camptothecins are alkaloids extracted from the Asian tree *Camptotheca acuminata*. Its synthetic and semisynthetic analogs containing the lactone ring necessary for activity with improved water solubility are topotecan and irinotecan. Metabolites such as *N*-desmethyl-topotecan, topotecan-*O*-glucuronide and *N*-desmethyl topotecan-*O*-glucuronide were found in clinical urine samples. Irinotecan is bioactivated by carboxyl esterase to the active metabolite SN-38. SN-38G is actively secreted into bile by the canalicular multispecific organic anion transporter (cMOAT). Deconjugation of SN-38 by intestinal flora appears necessary for the enterohepatic recirculation of SN-38. Irinotecan is also metabolized by CYP3A to numerous relatively inactive metabolites, including aminopentancarboxylic acid (APC) produced by CYP3A4-mediated oxidation of the terminal piperidine ring. NB-506 is a derivative of the indolocarbazole antibiotic BE-13793C isolated from *Actinomyces*. It showed potent topoisomerase I inhibition and antitumor activity. Metabolism of NB-506 is species-specific. The deformylated metabolite

ED-501 is active. The enzyme involved in the conversion of NB-506 to ED-501 in plasma is a rodent-specific serine enzyme. Ecteinascidin-743 is a marine tetrahydroisoquinoline alkaloid isolated from the Caribbean tunicate *Ectenascidia turbinata*. It exhibited potent antitumor activity. Etoposide and teniposide are topoisomerase II inhibitors, used in the treatment of adult and pediatric malignancies. Etoposide is primarily excreted unchanged in urine while teniposide is extensively metabolized in the liver. Several metabolites have been identified in humans, including products of hydrolysis of the lactone ring and the glycosidic bond, glucuronide conjugates, *O*-demethylated products and their corresponding glucuronides (30-31).

Tubulin-binding Drugs

Taxanes, a unique class of agents with a broad spectrum of clinical activity, act by binding to tubulin, producing unnaturally stable microtubules and subsequent cell death. Taxanes are metabolized in the liver by CYP450 enzymes with hepatobiliary excretion as the major route of elimination. The known metabolites are either inactive or less potent than the parent compound. Modifications of critical C10 and C3 positions of the taxane framework led to the development of analogs having better activity *in vivo* than the parent compound. *Vinca Alkaloids*, act by preventing normal microtubule formation in dividing cells. Vinca alkaloids are largely metabolized via P450 enzymes and eliminated via the hepatobiliary system. Desacetyl vinblastine and desacetyl-navelbine have been identified as metabolites of vinblastine and navelbine, respectively. The involvement of the CYP3A subfamily in vinblastine and vindesine metabolism was determined by Zhou-Pan et al. The ester hydrolysis product, 17-desacetylvinblastine has been characterized as an *in vivo* metabolite of vinblastine. Vincristine also undergoes metabolic transformation/inactivation by horseradish peroxidase, human serum copper oxidase and ceruloplasmin producing *N*-formylcatharinine, a metabolite at least 118 times less active than the parent compound (32-33)

Drugs affecting endocrine function

Lonning and Lien have reviewed the metabolism of several drugs affecting endocrine function, including glucocorticoids, estrogens, antiestrogen, progestins, androgens, antiandrogens, gonadotropin releasing hormone agonists and antagonists, aromatase inhibitors, and adrenocortical suppressors. *Tamoxifen*, the major therapeutic agent

for the treatment of hormone-dependent breast cancer, is extensively metabolized by hepatic CYP450, forming a reactive intermediate that binds irreversibly, to proteins and DNA. The major metabolite detected in human serum is *N*-desmethyltamoxifen, other metabolites are 4-hydroxytamoxifen, *N*-desdimethyltamoxifen and a side-chain primary alcohol. *N*-desmethylation of tamoxifen is catalyzed liver CYP3A and the 4-hydroxylation is catalyzed by human CYP2C8 (34).

New target-based drugs

New target-based drugs, also known as non-cytotoxic or cytostatic drugs were believed to be selective in terms of their molecular effects and therefore to have minimal toxicity (35). New target-based drugs include inhibitors of signal transduction, cyclin-dependent kinases, and angiogenesis.

Inhibitors of signal transduction

One family of molecules critical for malignant transformation and metastasis are the peptide growth factors that regulate cell entry into, and progression through the cell cycle by binding to membrane receptor tyrosine kinases (RTKs). RTKs transmit signals to the nucleus through an intricate network of adaptor and signaling molecules. Various active quinazole derivatives have been synthesized. They compete at specific ATP binding sites of the catalytic domains of the TKs, or bind to the extracellular domain of the RTK. ZD 1839, an anilinoquinazoline is a highly specific reversible EGF-RTK inhibitor that blocks signal transduction and causes antiproliferative effects. STI-571 is designed as a specific Bcr-Abl TKI gene that showed a potent activity against chronic myeloid leukemia (36).

Inhibitors of Cyclin-dependent kinases

Bryostatins

Bryostatins shows potent and broad activity against human cancer cell lines and in murine xenograft tumor models *in vivo*. Bryostatin 1, is the most potent member of this class it potently binds and activates protein kinase C. Currently, there are at least 20 known natural bryostatins, in which oxygens at C₁, C₁₉ and C₂₆ seem to be required for binding to PKC. Flavopiridol is a semi synthetic flavone that potently inhibits cyclin-dependent kinases causing cell arrest at G1 or G2. Flavopiridol showed potent antiproliferative and cytotoxic activity against a variety of cell types *in vitro*, including breast cancer cells, prostate carcinoma cells, human lung, and head and neck cancer cells

among others. Glucuronidation is the major route of metabolism (37).

Angiogenesis inhibitors

Angiogenesis is the formation of new blood vessels and involves a sequence of complex events with consequences in many physiological and pathologic processes. Cancerous tumors depend heavily on inducing angiogenesis to supply oxygen and nutrients necessary for survival. Thus, blockade of angiogenesis is a logical approach to inhibit tumor proliferation and metastasis (38).

Inhibitors of endothelial cell growth

These include Squalamine, endostatin TNP-470 and thalidomide. Squalamine shows promise as an antiangiogenic agent in developing malignant tumors. Its effect is mediated, at least in part, by the blockade of mitogen-induced proliferation and migration of endothelial cells, thus preventing neovascularization of the tumors. Angiostatin and Endostatin, two endogenously produced proteins, were shown to have antiangiogenic properties. Endostatin, a carboxy-terminal fragment of collagen XVIII specifically suppresses endothelial cell proliferation and increases the apoptotic rate of the tumor cells. *TNP-470*, showed a wide variety of anti-tumor activities by arresting cell cycle that prevents endothelial cells from entering the G1 phase, resulting in a decreased proliferation. TNP-470 undergoes rapid and extensive metabolism via esterases, epoxide hydrolases and glucuronidation reactions in human hepatocytes. *Thalidomide* had successfully used as anti-tumor agent against multiple myeloma. Thalidomide is currently in phase I/II trials for advanced melanoma; phase II for ovarian cancer, Kaposi's sarcoma, liver cancer, multiple myeloma, brain tumors and multiple myeloma; and in phase III for non-small cell lung, non metastatic prostate and renal cancer. The metabolic or hydrolytic products of thalidomide are responsible for its various biological effects. The initial hydrolysis products are phthalimidoglutaramic acid and carboxybenzamidoglutarimide. The former was angiogenic, while the latter was inactive (39).

Conclusion

Several drugs have recently been introduced into cancer chemotherapy including: inhibitors of chromatin function, target-based inhibitors of signal transduction, cyclin-dependent kinases and angiogenesis inhibitors. The time course and

duration of action of drugs used in cancer chemotherapy are greatly influenced by the molecular and biochemical properties of enzymes associated with their metabolism. Current knowledge of the molecular biology and biochemistry of phase I drug metabolizing enzymes (cytochrome P450, flavin-containing monooxygenases and xanthine oxidoreductases, NADPH, quinone oxidoreductases, and aldehyde and dihydropyrimidine dehydrogenases), and phase II enzymes (glucuronosyl-, sulfo-, N-acetyl-, and glutathione transferases, and hydrolases). New target-based drugs like inhibitors of signal transduction, cyclin-dependent kinases, and angiogenesis are believed to be selective in terms of their molecular effects and therefore have minimal toxicity.

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