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EXPERT OPINION

Drug transport and metabolism of novel anticancer drugs

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Many anticancer drugs need to be metabolized in order to exert their action, including the antitumor effect but unfortunately metabolism may also result in the formation of toxic metabolites. Metabolism may also change the physico-chemical properties of a molecule so that it may or may not become a substrate for one of the efflux pumps, such as the ABC transporters, including P-glycoprotein, the multidrug resistance proteins and the breast cancer resistance protein (BCRP) [1]. This can lead to unwanted accumulation in normal tissues resulting in toxicity. These usually poor physico-chemical properties [2] also determine whether a compound will be a substrate for one of the many influx transporters, such as the organic cation transporters or the organic anion transporters.

Although metabolism was recognized to be an important aspect in tumor development (e.g., according to the Warburg hypothesis) and drug metabolism, these properties tended to be neglected in drug development in the last decade of the twentieth and the first of twenty-first century. Early anticancer drug development focused on the increased need of tumor cells for DNA synthesis, leading to drugs that alter the synthesis of DNA and RNA precursors, such as the antimetabolites [3], or drug affecting the DNA structure, such as alkylating agents, anti-tubulins and platinum analogs. Both serendipity and rational drug design played major roles in drug development with nitrogen mustards and methotrexate, respectively, as classical examples [4]. However, for all these drugs, possibly by their nature, it was recognized that metabolism plays a major role in antitumor activity, resistance and toxicity. In the early stages of the development of protein kinase inhibitors, the focus was on the target and only protein kinase inhibitors were considered as targeted therapy or even molecular targeted therapy, neglecting that the classical antifolate methotrexate has only one target, dihydrofolate reductase [5], and that hormonal therapy was targeted against, for example, the estrogen receptor [6]. Moreover, one of the major molecules in the cell, DNA, is targeted by drugs like cisplatin and oxaliplatin [7], which can be considered as an early example of molecular targeted therapy. Neglecting the important role of metabolism in the pharmacology of any drugs was a major drawback in the early development of protein kinase inhibitors, resulting in poorly designed clinical trials and unexpected serious or even life-threatening toxicities. Moreover, most of the targeted therapies appeared to be multitargeted [8], and only recently it is being recognized that targeted therapy might be effective in several tumors because of its multitargeted nature [2]. Tumor cells are characterized by the presence of multiple altered signaling pathways, so that protein kinase inhibitors can lead to an un-intended paradoxical activation of other signaling pathways, either directly or via feedback loops [2]. This robustness can be considered a hallmark of a cancer cell. Therefore a multitargeted protein kinase inhibitor is more likely to be effective than a specific mono-targeted drug [8]. Only tumors that are dependent on one specific mutation or translocation (e.g., bcr-abl) are likely to be sensitive to a relatively specific protein kinase inhibitor, such as imatinib [9], whose efficacy is negatively influenced by its metabolism and by being a substrate for efflux transporters [10]. Crizotinib is targeted against ALK, but in addition shows favorable pharmacokinetics [11]. Another advantage can be achieved when the metabolite of a drug would inhibit another target,

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preferably tumor specific. However, metabolites often result in toxicity by inhibition of the target or of off-target protein kinases in normal tissues, with rash as typical example of EGFR inhibition in skin [12].

This special issue of Expert Opinion on Drug Metabolism and Toxicology aims to critically review the role of metabolism and transport of novel anticancer agents, as well as to evaluate novel insights on the regulation of metabolic enzymes on currently used cytotoxic drugs. In various papers, the differential roles of Phase I (oxidation) and II enzymes (conjugation, glucuronidation) in activation and inactivation are being highlighted. The role of metabolism is highlighted for sorafenib, whose properties change upon metabolism so that it becomes a substrate for the efflux transporter BCRP, which results in a different pharmacokinetic profile [13]. Such properties need to be taken into account in sophisticated mathematical models that are currently more frequently being applied for drug development [14,15]. Other aspects that are highlighted in this issue is an overview of the physicochemical properties of the various protein kinase inhibitors [16], which can lead to specific accumulation in cellular organelles (e.g., sunitinib in lysosomes), preventing them from attacking their target [17]. Other papers describe the important role of degradation in preventing drug toxicity (e.g., gemcitabine and 5-fluorouracil [5FU]) [18,19], but also limiting the antitumor activity. Interestingly, a high activity of cytidine deaminase reduces the toxicity of gemcitabine (and its efficacy), but may lead to a better efficacy (and sometimes increased toxicity) of the 5FU prodrug capecitabine. Splicing is a well-known process leading to correct formation of a protein; however, several physiological processes are regulated by proteins formed by the process of alternative splicing [20]. This process can be tissue specific but also altered in tumors, leading to altered (or decreased) drug activation resulting in drug resistance. The role of hepatic metabolism in drug pharmacology (both the pharmacokinetics and pharmacodynamics) is illustrated for the family of taxane analogs [21]. Other important issues that are covered in this special issue are the role of gender in drug metabolism, age, co-medication, alternative medicine and interethnic differences [6,19]. The latter aspects are gaining much more importance in the development of personalized therapy, as drug metabolism has been shown to be different between various populations. It has been shown that important genetic polymorphisms exist between Asian and Caucasian population as well as between Caucasians and African black populations [19,22]. This will affect hormonal therapy, cytotoxic therapy as well as tyrosine kinase inhibitors. Obesity is a lifestyle factor that not only increases the chance of developing cancer but also influences drug metabolism, while drugs may accumulate in fatty tissues affecting their pharmacokinetics. Interestingly, erlotinib's metabolism is increased by smoking through induction of CYP450 enzymes, but smoking may also reduce the effect of other drugs such as irinotecan and gemcitabine [23,24].

In summary, this special issue of Expert Opinion on Drug Metabolism and Toxicology not only highlights the important role of drug metabolism in the efficacy of novel anticancer agents, but also puts emphasis on unexpected effects of metabolism on currently used medication, especially when they are used in combination with novel drugs.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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