LINK TO ORIGINAL ARTICLE

The ABC of glycosylation

Paola Perego, Laura Gatti and Giovanni L. Beretta

We read with great interest the Opinion article by Jamie Fletcher and colleagues, ABC transporters in cancer: more than just drug efflux pumps. *Nature Rev. Cancer*. **10**, 147–156 (2010), recently published in *Nature Reviews Cancer*[1]. The authors underline innovative aspects regarding the role of ATP binding cassette (ABC) transporters that — besides contributing to drug resistance[2] — seem to be important for the development of tumours. Accumulating evidence shows that the expression of specific ABC transporters is associated with tumour-initiating cells and cancer stem cells (CSCs)[3], implying that the limited efficacy of chemotherapy might reflect the failure to eliminate CSC-expressing ABC transporters. However, expression by CSC would not necessarily mean that ABC transporters are implicated in cancer initiation and/or progression because their expression might be controlled by other proteins that function as master regulators. Nonetheless, ABC transporter expression has been correlated with progression and a more aggressive tumour phenotype[4,5].

In addition to these concepts, we think that post-translational modifications of ABC transporters, specifically glycosylation, is an important field of reasearch[6] through which new insights into the function of ABC transporters in tumorigenesis should be forthcoming. That glycosylation defects on ABC transporters, in particular ABCC1 (also known as MRP1), have consequences has been provided by a study showing the mislocalization of multidrug transporters in cisplatin-resistant cancer cell lines[7]. Interestingly, glycosylation might regulate ABC transporter levels, as altered glycosylation of ABCG2 (also known as BCRP) results in increased degradation[8]. Indeed, N-linked glycans are thought to be crucial regulators of the stability of ABCG2 in the endoplasmic reticulum[8,9]. In fact, N-glycosylated wild-type ABCG2 is degraded in lysosomes, whereas misfolded mutant proteins have been shown to undergo ubiquitin-mediated degradation in the proteasome[10,11]. We have recently observed that increased levels of glycosylation-defective ABCC1 and ABCC4 are associated with resistance to platinum compounds in ovarian carcinoma cell lines[12]. This phenotype is not due to mutations in the putative N-glycosylation sites of these transporters, but is instead related to the reduced expression of two glycosyltransferases, GNPTG (which accounts for the first step in the biosynthesis of N-glycans) and MGAT5 (which catalyses the addition of mannose to proteins). In keeping with this, a protective role has been ascribed to the glycosylation of ABCB1 (also known as P-glycoprotein), which can be shut down by statins[13], thereby suggesting new therapeutic options. Therefore, we propose that glycosylation is a relevant regulatory mechanism of ABC transporter expression and should be considered so that we can better understand the contribution of transporters to both drug resistance and tumour initiation and progression.

Paola Perego, Laura Gatti and Giovanni L. Beretta are at the Department of Experimental Oncology and Molecular Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Via Amadeo 42, 20133 Milan, Italy.
Correspondence to P.P.
e-mail: Paola.Perego@istitutotumori.mi.it

doi:10.1038/nrc2789-c1

Acknowledgements
The authors thank the Associazione Italiana per la Ricerca Sul Cancro, Milan, Italy, for financial support.

Competing Interests
The authors declare no competing financial interests.

1. Fletcher, J. I., Haber, M., Henderson, M. J. & Norris, M. D. ABC transporters in cancer: more than just drug efflux pumps. *Nature Rev. Cancer* **10**, 147–156 (2010).
2. Gillet, J.-P., Efferth, T. & Remacle, J. Chemotherapy-induced resistance by ATP-binding cassette transporter genes. *Biochem. Biophys. Acta* **1775**, 237–262 (2007).
3. Gatti, L., Beretta, G. L., Cossa, G., Zunino, F. & Perego, P. ABC transporters as potential targets for modulation of drug resistance. *Mini Rev. Med. Chem.* **9**, 1102–1112 (2009).
4. Faggad, A. *et al.* Expression of multidrug resistance-associated protein 1 in invasive ovarian carcinoma: implication for prognosis. *Histopathology* **54**, 657–666 (2009).
5. Leonard, G. D., Fojo, T. & Bates, S. E. The role of ABC transporters in clinical practice. *Oncologist* **8**, 411–424 (2003).
6. Richert, N. D., Aldwin, L., Nitecki, D., Gottesman, M. M. & Pastan, I. Stability and covalent modification of P-glycoprotein in multidrug-resistant KB cells. *Biochemistry* **27**, 7607–7613 (1988).
7. Liang, X. J., Shen, D. W., Garfield, S. & Gottesman, M. M. Mislocalization of membrane proteins associated with multidrug resistance in cisplatin-resistant cancer cell lines. *Cancer Res.* **63**, 5909–5916 (2003).
8. Wakabayashi-Nakao, K., Tamura, A., Furukawa, T., Nakagawa, H. & Ishikawa, T. Quality control of human ABCG2 protein in the endoplasmic reticulum: ubiquitination and proteasomal degradation. *Adv. Drug Deliv. Rev.* **61**, 66–71 (2009).
9. Nakagawa, H. *et al.* Disruption of N-linked glycosylation enhances ubiquitin-mediated proteasomal degradation of the human ATP-binding cassette transporter ABCG2. *FEBS J.* **6**, 7237–7252 (2009).
10. Furukawa, T. *et al.* Major SNP (Q141K) variant of human ABC transporter ABCG2 undergoes lysosomal and proteasomal degradations. *Pharm. Res.* **26**, 469–479 (2009).
11. Nakagawa, H. *et al.* Ubiquitin-mediated proteasomal degradation of non-synonymous SNP variants of human ABC transporter ABCG2. *Biochem. J.* **411**, 623–631 (2008).
12. Beretta, G. L. *et al.* Increased levels and defective glycosylation of MRPs in ovarian carcinoma cells resistant to oxaliplatin. *Biochem. Pharmacol.* **79**, 1108–1117 (2010).
13. Sieczkowski, E., Lehner, C., Ambros, P. F. & Hohenegger, M. Double impact on p-glycoprotein by statins enhances doxorubicin cytotoxicity in human neuroblastoma cells. *Int. J. Cancer.* **126**, 2025–2035 (2010).