BJP BRITISH JOURNAL OF PHARMACOLOGY

BPS BRITISH PHARMACOLOGICAL SOCIETY

British Journal of Pharmacology (2009), 157, 1172–1174

0007-1188/09
www.brjpharmacol.org

COMMENTARY

Escaping immune surveillance in cancer: is denbinobin the panacea?

Tapiwanashe Magwere

Leeds Institute of Molecular Medicine (LIMM), St. James's University Hospital, Leeds, UK

The bane of anti-cancer therapy is usually the development of resistance to apoptosis in malignant cells. Identification of strategies to re-sensitize cancer cells to apoptosis has now become a top priority in anti-cancer research. Denbinobin is a novel, naturally occurring phenathroquinone isolated from orchids of the genus *Dendrobium* that has remarkable anti-cancer activities demonstrated both *in vitro* and *in vivo*. Recently denbinobin has been shown to diminish the levels of expression of the decoy receptor-3 and also to act synergistically with Fas ligand to induce apoptosis in a pancreatic adenocarcinoma cell line. There is hope that denbinobin could be developed as an adjuvant in combination therapies aimed at killing cancers that rely on decoy receptors to evade the host's immune surveillance.
British Journal of Pharmacology (2009) **157,** 1172–1174; doi:10.1111/j.1476-5381.2009.00286.x

This is a Commentary on the Research Paper in this issue of *BJP* entitled *Combined treatment with Denbinobin and Fas ligand has a synergistic cytotoxic effect in human pancreatic adenocarcinoma BxPC-3 cells* (Yang *et al.*, pp. 1175–1185). To view this article visit http://www3.interscience.wiley.com/journal/121548564/issueyear?year=2009

Keywords: cancer; pancreatic cancer; death receptor; Fas ligand; decoy receptor; immune surveillance; apoptosis; denbinobin

Abbreviations: DcR1, 2, 3, decoy receptors 1, 2, 3; DR 3, 4, 5, death receptor 3, 4, 5; Fas L, Fas ligand; TNF, tumour necrosis factor

The immune system features prominently among the body's natural defences against cancer; cytotoxic T-cells, natural killer cells and macrophages target cancer cells for destruction through recognition of specific molecules or antigens on their surfaces (Swann and Smyth, 2007). One mechanism by which immune cells effect tumour cell killing is through secreting (or expressing on their cell surface) 'death ligand' molecules that bind to 'death receptors' on target cells to initiate apoptosis. Death receptors belong to the tumour necrosis factor (TNF) receptor superfamily of which the best known are TNFR1, Fas and the death receptors DR3, DR4 and DR5 (Ashkenazi and Dixit, 1998). These receptors have in common a homologous cytoplasmic sequence (the death domain) that interacts with, and activates, initiator caspases (e.g. caspase 8) to trigger apoptosis (Ashkenazi and Dixit, 1998). In addition to the death receptors, however, structurally related molecules called decoy receptors (DcRs; DcR1, DcR2 and DcR3) are also present on target cells and these compete with death receptors for death ligand binding (Ashkenazi and Dixit, 1999). Because DcRs lack the cytoplasmic death domain, their binding to death ligands generally leads to inhibition of ligand-induced apoptosis.

Correspondence: Tapiwanashe Magwere, Leeds Institute of Molecular Medicine (LIMM), St. James's University Hospital, Cancer Research Building, Beckett Street, Leeds LS9 7TF, UK. E-mail: t.magwere@leeds.ac.uk
Received 17 February 2009; accepted 27 February 2009

The binding of Fas ligand (FasL) to the Fas receptor is an important trigger for apoptosis, but evidence has shown that FasL-triggered apoptosis is often inhibited by the over-expression of DcR3 in some cancers (Pitti *et al.*, 1998), and such over-expression is associated with poor prognosis in some patients (Takahama *et al.*, 2002). The concept of targeting the DRs to induce cell death in tumours is very attractive because they have direct access to the cell's apoptotic machinery, but severe constraints are imposed by the toxic side effects of the biological agents used (Ogasawara *et al.*, 1993). As such, attempts at identifying strategies to circumvent the DcR3-induced malignancy and ameliorating the toxic side effects of DR-targeted therapies have become important aims in cancers known to over-express DcR3, such as pancreatic adenocarcinoma.

Pancreatic carcinoma ranks among the most malignant of human cancers that easily acquires resistance to cytotoxic chemotherapy with gemcitabine/fluoropyrimidine, platinum-based agents or radiation (O'Reilly and Abou-Alfa, 2007) possibly through over-expression of DcR3 (Tsuji *et al.*, 2003). In this issue of the *British Journal of Pharmacology*, Yang *et al.* (2009) describe a novel and promising strategy that has potential for overcoming DcR3-induced resistance to apoptosis in pancreatic cancer (see Figure 1). Using a carefully selected BxPC-3 pancreatic cell line that over-expresses DcR3 (and hence highly resistant to FasL), these authors showed that treatment of these cells with denbinobin (5-hydroxy-3,7-dimethoxy-1,4-phenathroquinone) dose-dependently

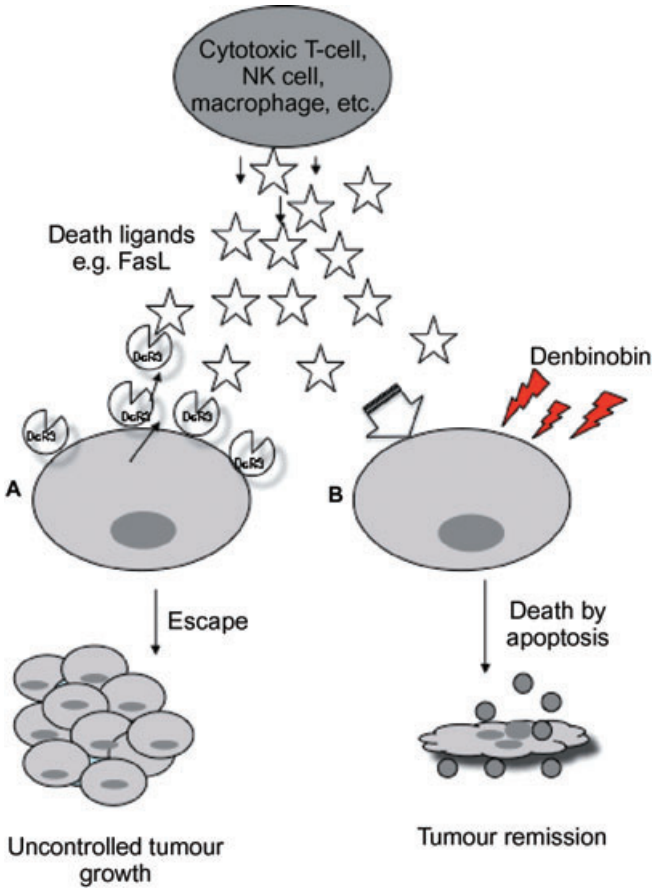

Figure 1 A diagram of how denbinonin can be used to overcome DcR3-induced apoptosis resistance in pancreatic adenocarcinoma cells. (A) Tumour cells over-expressing DcR3 can evade being killed by the immune system whereas (B) denbinobin treatment down-regulates DcR3 expression and synergistically enhances death ligand-induced apoptosis. DcR3, decoy receptor-3; FasL, Fas ligand; NK, natural killer cells.

decreased DcR3 expression by up to 80% without affecting cell viability. When Yang *et al*. combined a similar dose of denbinobin with soluble FasL treatment in BxPC-3 cells, they observed a synergistic enhancement of cell death: the degree of cell death achieved was much greater than that obtained with either agent alone.

What is interesting about this group's findings is that denbinobin appears to sensitize BxPC-3 cells to apoptosis not by increasing the levels of Fas expression on their surfaces, nor by activation of caspases, but by increasing the cellular levels of the apoptosis-inducing factor and decreasing the levels of DcR3. This ability of denbinobin to stimulate caspase-*independent* apoptosis potentially makes it an attractive candidate for multi-targeted combination therapies with agents that stimulate caspase-*dependent* apoptosis. Excitingly, denbinobin could turn out to be the sought-after panacea for controlling the growth of cancers that depend on decoy receptors to evade the host's immune system.

Denbinobin is a naturally-occurring 1,4-phenathroquinone extracted from *Ephemerantha lonchophylla* but it has also been isolated from other orchid species belonging to the genus *Dendrobium* (Lee *et al*., 1995). It is somewhat disappointing, however, to note that despite the excitement surrounding this new compound as a result of the work by Yang *et al*. (2009) and others, very little is yet known about its systemic effects which may put limitations to its clinical applications. The only *in vivo* data available on the anti-tumour effects of denbinobin were obtained in athymic nude mice bearing human colon COLO-205 tumour xenografts where tumour shrinkage by up to 68% was observed following 50 $mg \cdot kg^{-1}$ intraperitoneal injections (Yang *et al*., 2005). At present it is still a matter of conjecture as to whether denbinobin could have the same tumour-shrinking effects in human pancreatic cancer *in vivo*. There is also need to bear in mind that the observations of synergism between denbinobin and FasL were made *in vitro* (Yang *et al*., 2009), and that the response of cancer cells to the same treatment combination *in vivo*, under hypoxic conditions, might differ. Furthermore, there is still a mystery surrounding the mechanism by which denbinobin depresses the expression of DcR3 in pancreatic cancer cells. Although Yang *et al*. have shown that denbinobin stimulates a caspase-*independent* apoptotic mechanism in BxPC-3 cells, it has also been shown to trigger caspase-*dependent* apoptosis in other cancers (Kuo *et al*., 2008). Such cancer type-specific effects again restrict the potential application of denbinobin in treating certain types of cancer. All these issues need to be adequately addressed before denbinobin can be integrated fully into the anti-cancer armamentarium.

Nevertheless, the work of Yang *et al*. (2009) heralds the advent of a new and promising strategy in the fight against pancreatic cancer. It is both exciting and reassuring to note the addition of yet another plant natural product to the ever-growing arsenal of anti-cancer agents. Perhaps denbinobin is only the first of a futuristic new class of anticancer 'dendrobicides' to come from the Asian *Dendrobium* orchids.

Conflict of interest

None declared.

References

Ashkenazi A, Dixit VM (1998). Death receptors: signaling and modulation. *Science* **281** (5381): 1305–1308.

Ashkenazi A, Dixit VM (1999). Apoptosis control by death and decoy receptors. *Curr Opin Cell Biol* **11** (2): 255–260.

Kuo CT, Hsu MJ, Chen BC, Chen CC, Teng CM, Pan SL *et al*. (2008). Denbinobin induces apoptosis in human lung adenocarcinoma cells via Akt inactivation, Bad activation, and mitochondrial dysfunction. *Toxicol Lett* **177** (1): 48–58.

Lee YH, Park JD, Baek NI, Kim SI, Ahn BZ (1995). In vitro and in vivo antitumoral phenanthrenes from the aerial parts of *Dendrobium nobile*. *Planta Med* **61** (2): 178–180.

O'Reilly EM, Abou-Alfa GK (2007). Cytotoxic therapy for advanced pancreatic adenocarcinoma. *Semin Oncol* **34** (4): 347–353.

Ogasawara J, Watanabe-Fukunaga R, Adachi M, Matsuzawa A, Kasugai T, Kitamura Y *et al*. (1993). Lethal effect of the anti-Fas antibody in mice. *Nature* **364** (6440): 806–809.

Pitti RM, Marsters SA, Lawrence DA, Roy M, Kischkel FC, Dowd P *et al*. (1998). Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer. *Nature* **396** (6712): 699–703.

Swann JB, Smyth MJ (2007). Immune surveillance of tumors. *J Clin Invest* **117** (5): 1137–1146.

Takahama Y, Yamada Y, Emoto K, Fujimoto H, Takayama T, Ueno M *et al*. (2002). The prognostic significance of overexpression of the decoy receptor for Fas ligand (DcR3) in patients with gastric carcinomas. *Gastric Cancer* **5** (2): 61–68.

Tsuji S, Hosotani R, Yonehara S, Masui T, Tulachan SS, Nakajima S *et al*. (2003). Endogenous decoy receptor 3 blocks the growth inhibition signals mediated by Fas ligand in human pancreatic adenocarcinoma. *Int J Cancer* **106** (1): 17–25.

Yang CR, Guh JH, Teng CM, Chen CC, Chen PH (2009). Combined treatment with Denbinobin and Fas ligand has a synergistic cytotoxic effect in human pancreatic adenocarcinoma BxPC-3 cells. *Br J Pharmacol* **157**: 1175–1185.

Yang KC, Uen YH, Suk FM, Liang YC, Wang YJ, Ho YS *et al*. (2005). Molecular mechanisms of denbinobin-induced antitumorigenesis effect in colon cancer cells. *World J Gastroenterol* **11**: 3040–3045.

This is a Commentary on the Research Paper in this issue of *BJP* entitled *Combined treatment with Denbinobin and Fas ligand has a synergistic cytotoxic effect in human pancreatic adenocarcinoma BxPC-3 cells* (Yang *et al*., pp. 1175–1185). To view this article visit http://www3.interscience.wiley.com/journal/121548564/issueyear?year=2009