PHARMACOLOGY

Transporter for milk toxins

Many medicines, carcinogens and environmental contaminants accumulate in milk — a potential health risk for breast-fed infants and those fond of dairy food. Jonker and colleagues have identified the transporter responsible for the secretion of several drugs and toxins into milk in mice, cows and humans.

The authors were studying the breast cancer resistance protein ABCG2 (also known as BCRP), an ATP-binding cassette drug transporter. This transporter expels drugs, carcinogens and environmental toxins across the cell membrane, which can lead to multidrug resistance in cancer cells. Its substrates are many and varied, including the potent dietary mutagen PhIP (2-amino-1-methyl-6-phenylimidazol[4,5-*b*] pyridine); topotecan, a cancer drug; cimetidine, a common treatment for ulcers and heartburn; and acyclovir, an antiviral drug.

The presence of ABCG2 in the epithelia of the intestine, kidney and bile canal indicates that this transporter helps to limit toxins in the body, getting rid of them through several excretion routes. But Jonker and colleagues found the mouse ABCG2 protein at high levels in the mammary epithelia during pregnancy and lactation. By contrast, virgin or non-lactating mice had little ABCG2 in the mammary epithelia. There is a similar pattern in cows and humans, with ABCG2 being highly expressed in lactating mammary glands, but absent from non-lactating ones.

To test whether this transporter might be responsible for the secretion of toxic compounds into milk, the researchers injected lactating wild-type and *Abcg2*-null mice with PhIP or topotecan. In the wild-type mice, both compounds were concentrated into the milk, unlike the knockout mice, where there was no secretion of either compound. Moreover, giving the ABCG2 inhibitor GF120918 to the wild-type mice also blocked secretion of topotecan into their milk.

Why a transporter that usually has a protective role, eliminating harmful compounds from the body, also secretes toxins to a suckling infant is hard to understand. That the presence of ABCG2 in the mammary gland has been conserved from mice to cows and humans implies an important role, and the authors speculate that the transporter might also secrete nutrients into milk, compensating for the risk from toxin contamination. They note, however, that the suckling pups of *Abcg2*-null mothers did not seem to be malnourished.

The findings have several useful implications. ABCG2 substrates might well accumulate in milk and their use should probably be restricted for breast-feeding mothers, and possibly for dairy cattle. Conversely, there might be cases where the transfer of drugs through milk is desirable. For instance, acyclovir, an antiviral used to treat opportunistic viral infections in HIV-positive individuals, is also an ABCG2 substrate that is concentrated in milk, and using this delivery route might reduce transmission of viruses from mother to baby.

Helen Dell

References and links

ORIGINAL RESEARCH PAPER Jonker, J. W. *et al.* The breast cancer resistance protein BCRP (ABCG2) concentrates drugs and carcinogenic xenotoxins into milk. *Nature Med.* 30 Jan 2005 (doi:10.1038/nm1186)

TRIAL WATCH

Auroras in the limelight

A Phase I clinical study for VX-680, a small-molecule inhibitor of Aurora kinases, has been initiated in patients with solid tumours. The open-label, dose-escalation study is designed to evaluate the safety and tolerability of VX-680 when administered in multiple cycles to patients with solid tumours that are refractory to chemotherapy.

Aurora-A, -B and -C comprise a family of serine/threonine kinases that regulate mitosis and are required for genome stability. They are overexpressed in many human tumour types, including colon cancer, breast cancer and leukaemia. Amplification of Aurora genes is associated with progression of colorectal cancer and poor prognosis in certain types of breast cancer.

The inhibitor VX-680, developed by Vertex Pharmaceuticals and Merck & Company, inhibits all members of the Aurora family. It has been shown to induce tumour regression in xenograft models of human pancreatic and colon cancer, and prolonged survival and induced sustained remission in a mouse model of human acute myelocytic leukaemia.

FURTHER READING Keen, N. & Taylor, S. Aurora-kinase inhibitors as anticancer agents. *Nature Rev. Cancer* **4**, 927–936 (2004)

WEB SITE

Vertex Pharmaceuticals Incorporated: http://www.vpharm.com/index.html

Zapping follicular lymphoma

Although advanced-stage follicular B-cell lymphoma is considered incurable, a study published in the *New England Journal of Medicine* reports that treatment with ^{131}I-tositumomab can induce prolonged clinical and molecular remission in patients.

Tositumomab is a mouse IgG2a monoclonal antibody that binds to CD20 on the surface of normal and malignant B cells. When labelled with iodine-131, it is believed to deliver ionizing radiation to lymphoma cells and kill them.

The study involved 76 patients with stage III or IV follicular lymphoma who received only a single 1-week course of ^{131}I-tositumomab therapy. Seventy-five percent (57) of these patients had a complete response, defined as the disappearance of all disease for at least 1 month or no change in radiographic abnormalities for at least 6 months. Furthermore, 80% of the complete-response patients also had a complete molecular response, as determined by the inability of PCR analysis to detect the t(14;18) translocation that is associated with this cancer. The 5-year progression-free survival for patients with a complete response was 77%.

The 5-year progression-free survival for all patients treated with ^{131}I-tositumomab was estimated at 59%, and the median progression-free survival was 6.1 years. These results compare favourably with current therapies — including unlabelled anti-CD20 antibody combined with chemotherapy. This treatment combination only yielded a complete response rate of 58% and a median survival time of 5 years, and must be administered over a much longer time period with highly toxic side effects. By contrast, the only side effect of a single treatment or ^{131}I-tositumomab was temporary B-cell depletion, with no apparent clinical consequences.

ORIGINAL RESEARCH PAPER Kaminski, M. S. *et al.* ^{131}I-tositumomab therapy as initial treatment for follicular lymphoma. *N. Engl. J. Med.* **325**, 441–449 (2005)

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