Newsfronts

No More Crying over Spoilt Milk

By identifying a key molecule involved in transporting toxic compounds out of the bloodstream and into mother's milk, researchers may have uncovered a new way to make breast-feeding safer and healthier.

Even with a wide variety of formulas available on the market, it is generally recognized that for a healthy infant there is no substitute for mother's milk. Not only does breast-feeding provide essential nutrients, but it has also proved to have a primary role in bolstering the infant's immune system. Unfortunately, breast milk can also provide a vehicle for considerably nastier compounds; research has found that breast milk can become a concentrated reservoir for many environmental toxins and carcinogens.

One such molecule is PhIP, a carcinogen that can be absorbed from cigarette smoke or well-done meat and that is known to accumulate markedly in breast milk. Alfred Schinkel and his colleagues at the Netherlands Cancer Institute (Amsterdam, the Netherlands) and Cardiff University (Cardiff, UK) were interested in identifying the mechanism by which PhIP and other compounds are deposited in milk. As they describe in a recent article from *Nature Medicine* (online 30 January, doi:10.1038/nm1186), they chose to focus on a drug transporter protein called ABCG2, which has previously been linked to drug resistance in breast tumors and is involved in the active elimination from the body of drugs and other toxic compounds in such organs as the intestine and kidney.

Schinkel's team found that, unlike other drug transporters, ABCG2 expression in the mammary glands increases markedly after the onset of lactation in mice, cows, and humans. They followed up by tracking the accumulation of PhIP in intravenously injected mice and found that, although PhIP was collecting in the milk of wild-type animals (a roughly 12-fold elevation relative to plasma levels), there was no such increase in mice in which Abcg2 had been knocked out. Similar experiments with the drug topotecan showed that an inhibitor specific for Abcg2 also blocked this transport process, with treated mice showing considerably reduced drug levels in their breast milk.

Although the authors express some puzzlement about the selective pressure that would favor a transporter that actively moves potentially toxic compounds into the mammary tissue, they nonetheless find their identification of this protein to be an encouraging development. Identifying chemicals that are ABCG2 substrates—and helping new mothers avoid them—could help make breast-feeding even healthier for infants than it was before.

—Michael Eisenstein

Hitting Viruses Where They Live

Drugs that operate on the targets of viral infection, rather than on viruses themselves, could provide an effective alternative for protecting against smallpox and other nasty pathogens.

Most of the therapeutic strategies currently developed to combat viruses target the particles themselves and focus on specific viral antigens or virus-specific enzymes. Ellis Reinherz of the Dana-Farber Cancer Institute (Boston, MA) saw potential in a different approach, which is directed toward cellular targets specifically involved in the process of viral infection. In the February issue of the *Journal of Clinical Investigation*, he and his colleagues present the outcome of one such investigation, an effort to develop new drugs to thwart poxvirus.

Facilitating the process of poxvirus pathogenesis are virus-specific growth factors that bind receptors on the surface of the host cell; for the smallpox growth factor (SPGF), this receptor is ErbB-1. Reinherz and his colleagues reasoned that this receptor might, therefore, make a viable target for blocking smallpox infection and thus began work on identifying drugs that can act on this receptor.

One of the compounds they identified, CI-1033, binds irreversibly and with high affinity to ErbB-1, and, although SPGF normally triggers a cascade of protein phosphorylation in cells expressing this receptor, treatment with CI-1033 decreases this signaling substantially. They also discovered that this compound reduced the size of plaques that formed in cell cultures infected with poxvirus, and data from these experiments suggested that CI-1033 was somehow blocking the release of mature virus particles from infected cells.

Reinherz's group continued their research with *in vivo* studies, using a variola-related poxvirus, vaccinia WR. Treatment with CI-1033 shortly before infection led to a marked improvement in the survival curve for intranasally infected mice, and the animals showed a significant decrease in the severity of their symptoms. There was even greater improvement in viral titer reduction and overall survival when CI-1033 was combined with a previously developed therapeutic antibody, anti-L1R, which targets a vaccinia-specific protein.

A final series of experiments tested the capacity of these therapies to protect mice after exposure—a scenario relevant to the perceived threat of smallpox as a potential bioweapon. After exposure to high doses of vaccinia for 2 days, mice then received various treatments; the antibody treatment contributed more substantially to overall survival, but the two treatments in combination led to significantly greater reduction in viral plaque-forming units and a general improvement in the animals' clinical condition. The inclusion of CI-1033 also led to a threefold augmentation of immune response in comparison with animals receiving anti-L1R alone.

These results, though preliminary, suggest an interesting new paradigm for drug design, one that could potentially bypass some of the limitations of pathogen-targeted treatments—such as the emergence of drug resistance—and provide a useful complement for existing pharmaceuticals.

—M.E.