for >25,000 new cancer cases per year in the USA.

'We are excited because this polymorphism is very frequent,' says Kaklamani. 'It is present in around one in ten people, compared with *BRCA1/2* mutations, which are present in one in 500 people.'

'The mutation appears to be one that could operate to alter cancer risk,' comments Neil Caporaso at the National Institute of Cancer (http://www.nci.nih.gov). He calls for another well designed molecular epidemiology study in a large population that focuses on the incidence of the 6A allele in one cancer at a time. 'It is intrinsic of a meta-analysis design that you want to see this conducted again now.'

Potential value

The identification of low-penetrance markers leads to a whole new set of research questions. 'The next step will be to see which combinations [of low-penetrance markers] can be used to most effectively predict who is going to develop disease and who is not, at least in the right environmental setting,' says David Weinberg at Fox Chase Cancer Center (http://www.fccc.edu). The researchers at Northwestern University are already trying to figure out whether the 6A allele has any impact on the breast cancer risk of individuals who harbour *BRCA1/2* mutations. Eventually, they want to develop a model that would predict the risk of breast cancer, for example, by taking into account several low-penetrance alleles. 'We hope that by identifying individuals who are at high risk of getting breast cancer, we will be able to more effectively screen them and prevent them from getting the disease,' says Kaklamani.

Genetic information of this sort might indeed prompt people to change their lifestyle, undergo cancer screening or take preventive medicine. It might also serve as an indicator of prognosis or response to therapy. Also, once scientists have nailed down a new susceptibility marker, they could find out more about the molecular mechanism of carcinogenesis. 'This may open up new pathways to chemoprevention or therapy,' concludes Caporaso.

'The potential value [of this sort of information] is high,' agrees Weinberg, 'and I think that is the spur to see what we can find out.' But he cautions that there is no guarantee for pay-off at the end. 'It may well be that the system is far more complicated. Understanding one aspect of it very well does not mean that we have seen enough of the whole process to be able to alter it in any meaningful way.'

References

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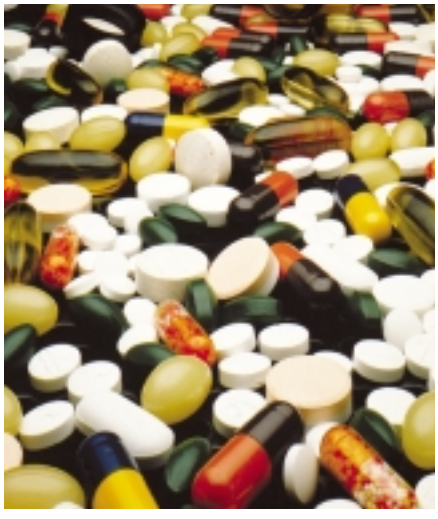
Drug designers learn their ABC

Dan Ferber, BMN News

Tough microbes and cancer cells use a family of related protein pumps called ABC transporters to fend off the drugs that are meant to poison them. Studying the components of those pumps could lead to rationally designed drugs to combat drug resistance, argues a German pathologist.



Multidrug resistance

Many drug-resistant microbes or cancer cells fend off the effects of a single chemical class of drugs. However, multidrug resistant microbes and cancer cells use protein pumps that can remove drugs of several chemical classes. As a result, the proteins make cells immune to the effects of a variety of antimicrobial or anticancer drugs.

ABC transporters are the most common class of such pumps. Structurally similar, ABC transporters help rid bacteria of antibiotics, fungal pathogens of antifungal drugs, malaria protozoans of quinine, and cancer cells of chemotherapy drugs such as anthracyclines and vinca alkaloids. Clearly the proteins represent an ancient strategy to defend cells from toxic chemicals, notes Hermann Lage

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of Humboldt-University Berlin (http://www.hu-berlin.de) [1]. 'There is an urgent need to understand the structure–function relationships of these efflux pumps,' says Lage. 'This knowledge may allow the rational design of new drugs that can inhibit or circumvent the pumps' activity.'

Structure of the ABC transporters

So far, researchers have experimentally determined only the structures of bacterial ABC transporters; the structures of ABC transporters from human cancer cells is unclear, says Rajendra Sharma, a biochemist at the University of Texas Medical Branch in Galveston (http://www.utmb.edu), who studies multidrug resistance.

But one thing is clear. 'They have special features which we should try to understand and then we can try to design drugs to block them,' said Sharma. That could get drugs inside bacteria or cancer cells and keep them there, which would make them more effective.

It would be particularly useful, he says, to block two key domains. One binds the drug and one enables the protein to attach to the cell membrane. 'If we could block the affinity of the transporter to the membrane, we could block the pump,' said Sharma.

New drugs that block ABC transporters could increase the effectiveness of cancer chemotherapy, according to Lage. Such drugs, called chemosensitizers, can be given in conjunction with standard chemotherapy drugs to cancer cells that survive chemotherapy. By blocking the pumps, the chemosensitizers would enable more chemotherapy drugs to enter the cell, perhaps enough to kill even the tough cancer cells.

Chemosensitizers

Such a strategy is worth pursuing, says Helen Coley, a pharmacologist at the University of Surrey, UK (http://www.surrey.ac.uk), who studies cancer drug resistance. The idea is not new, she says – the wave of research into chemosensitizers began in the 1980s when researchers discovered that a drug called verapamil leads resistant cancer cells to take up more chemotherapy drugs.

Since then, researchers have accumulated good evidence that ABC transporters are important in cancer cells *in vitro*. But it is not entirely clear that the pumps are what make cancer cells resistant to drugs *in vivo*. 'The hypothesis has never really been proven or disproven,' said Coley. Still, it is worth trying to design new drugs to block the pump proteins, she says. Drug resistance is extremely common, she notes, and forms the basis of drug failure in the treatment of many cancers, including breast, colon and lung tumours.

Tailoring to tumours

Understanding the detailed structure and function of ABC transporters will make it possible to design combinations of chemotherapy and chemosensitizing agents that are tailored to individual patients' tumours, predicts Lage. Researchers could use DNA microarrays to determine which ABC transporters were being expressed in tumour tissue, and use rationally designed drugs that specifically target those transporters.

That would solve a serious problem with the current crop of chemosensitizers, which target ABC transporters in healthy tissue, making the chemotherapy drugs more toxic, Coley says. A rationally designed chemosensitizer that targets the particular ABC transporter that is overexpressed in a particular tumour would be an improvement, she agrees. Lage 'is right to say we probably haven't designed the best chemosensitizers yet,' concluded Coley. 'I think we should keep trying.'

Reference

1 Lage, H. (2003) ABC-transporters: implications on drug resistance from microorganisms to human cancers. *Int. J. Antimicrobial Agents* 22, 188–199