Hunting for the real cancer genes

Martina Habeck, freelance writer

Researchers have pinpointed a cancer susceptibility gene that is present in over 10% of the healthy population and increases the risk of cancer by 26% [1]. This finding might be a step towards a future where genetic tests will reveal an individual's predisposition for common diseases and give people a chance to take preventive measures.

Disease susceptibilities

Genetic testing for complex disease susceptibilities is the subject of lively discussions, but it is far from being applied in clinical practice. Currently available genetic tests focus on the role of single-gene mutations that dramatically increase the risk of a specific disease ('high-penetrance' mutations). Examples in oncology include mutations in the *BCRA1* and *BRCA2* genes in breast cancer, the *APC* gene in colorectal cancer and the *HPC1* locus in prostate cancer.

However, these high-penetrance mutations are so rare that they account for less than 10% of all cancer cases. The majority of tumours appear to result from the cumulative effects of mutations that in themselves have relatively little impact on cancer risk. However, when they act in concert with each other, or in the presence of certain environmental risk factors, they can increase an individual's risk significantly.

Much research is now being conducted to uncover these low-penetrance genes, not just in cancer but also in other common diseases such as diabetes and hypertension. A variety of low-penetrance polymorphisms have already been reported. However, the findings are often controversial. 'To find statistically significant results, you need [studies with] large numbers of cases and controls,' says Virginia Kaklamani, lead author of a recent meta-analysis to investigate the cancer risk associated with a genetic variant of the gene coding for the type I TGF-β receptor (TGFBR1).

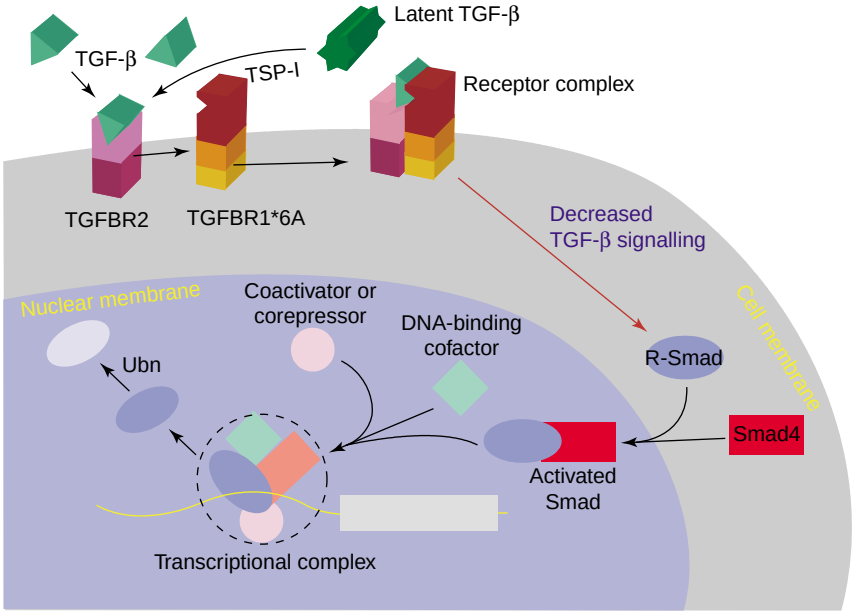

Figure 1. Possible consequences of altered TGF-β signalling. Cells produce and secrete latent TGF-β, which can be activated by thrombospondin-1 (TSP-I) to release the bioactive TGF-β protein. Active TGF-β binds to a cell-surface receptor complex comprised of type I (TGFBR1) and type II (TGFBR2) receptors; the receptor complex in turn activates the Smad proteins in the cytoplasm, which move into the nucleus where they induce complex mechanisms of gene regulation (ubn = ubiquitin). In healthy cells, TGF-β signalling leads to the inhibition of cell proliferation. However, both receptor proteins need to be intact for effective signalling. The 6A allele of the TGFBR1 gene (it codes for six instead of nine alanines in a polyalanine repeat) is associated with decreased growth-inhibitory activity – as a result, cells might proliferate more unrestrictedly. Figure reproduced, with permission, from reference [2] and supplied courtesy of Virginia Kaklamani (Northwestern University in Chicago; http://www.northwestern.edu).

The role of TGFBR*6A

To date, seven case-control studies have been published to see whether the 6A allele of TGFBR1 (TGFBR1*6A) (Figure 1) increases the risk for cancer, but the results have been mixed. To come up with more meaningful results, Boris Pasche, Kaklamani and colleagues at Northwestern University in Chicago (http://www.northwestern.edu), pooled the data from those case-control studies and looked at the incidence of the 6A allele in this much larger patient population. The result: the mutation increases the risk of cancer by 26%. More specifically, the risk of breast, ovarian or colon cancer is increased by ~50%. The scientists claim that the polymorphism could be responsible

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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.'

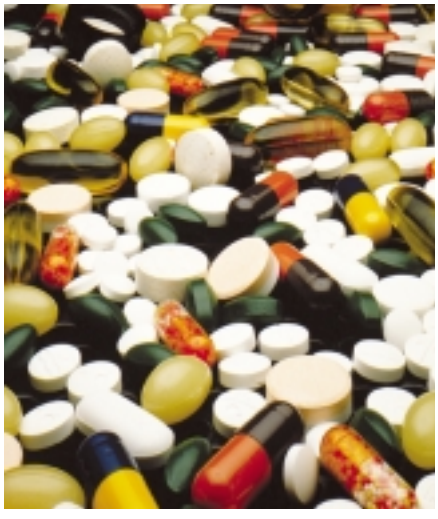
References

1 Kaklamani, V.G. *et al.* (2003) TGFBR1*6A and cancer risk: a meta-analysis of seven case-control studies. *J. Clin. Oncol.* 21, 3236–3243
2 Pasche, B. (2001) Role of transforming growth factor beta in cancer. *J. Cell. Phys.* 186, 153–168

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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