IN BRIEF

PHARMACOGENETICS

EGFR mutations in lung cancer: correlation with clinical response to Gefitnib therapy

Paez, J. G. *et al*. *Science* 29 Apr 2004 [epub ahead of print]

Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to Gefitinib

Lynch, T. J. *et al*. *N. Engl. J. Med.* **350**, 29 Apr 2004 [epub ahead of print]

Most patients with non-small cell lung cancer do not respond to the tyrosine kinase inhibitor gefitinib (Iressa; AstraZeneca), although those who do often have a dramatic clinical response. Two recent studies have identified similar point or deletion mutations in the epidermal growth factor receptor (EGFR) that could be predictive of which patients will benefit from gefitinib. Tumour biopsies from eight out of nine patients with gefitinib-responsive lung cancer carried these mutations, compared with none from seven non-responders. Paez *et al.* found *EGFR* mutations in 15 of 58 unselected tumours from Japan and 1 of 61 from the United States. Five out of five samples selected that had *EGFR* mutations were from treatment responders. The mutations are found in the ATP-binding pocket of the tyrosine kinase domain of EGFR and are associated with increased sensitivity to inhibition by gefitinib.

HIV-1

Structures of HIV-1 RT-DNA complexes before and after incorporation of the anti-AIDS drug tenofovir

Tuske, S. *et al*. *Nature Struct. Mol. Biol.* **11**, 469–474 (2004)

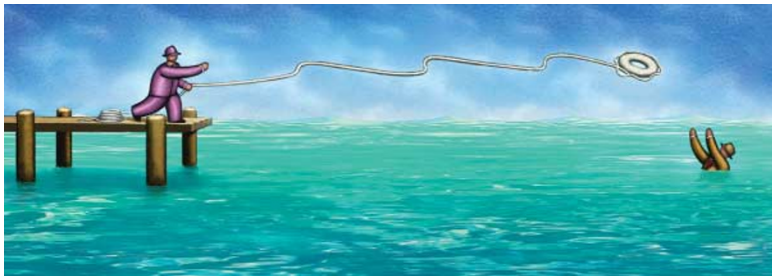
HIV-1 viruses do not readily develop resistance to the prodrug tenofovir disoproxil fumarate (Viread; Gilead), which inhibits a viral protein reverse transcriptase (RT). A recent study compared structures of RT with bound tenofovir, and it helps explain the unusually low resistance of HIV to tenofovir. The structures show that mutations in RT that could reduce tenofovir incorporation would also substantially diminish the natural function of the enzyme. Furthermore, incorporated tenofovir can escape 'correction' activity of RT by adopting several conformations, thereby moving out of the active site of the enzyme with the growing chain.

ANTISENSE

Determination of the role of the human Rnase H1 in the pharmacology of DNA-like antisense drugs

Wu, H. *et al. J. Biol. Chem*. **279**, 17181–17189 (2004)

Although it has been assumed that DNA-like antisense oligonucleotides (ASOs) cause target RNA reduction by binding to the target RNA and creating a DNA–RNA duplex that serves as a substrate for RNase H, definitive proof is lacking. By altering expression levels and cellular activity of RNase H1, the authors showed that RNase H1 is crucially involved in the effects of DNA-like ASOs. Furthermore, the data suggest that there might be other RNase H enzymes in mammalian cells that contribute to the activity of DNA-like ASOs.



ANTICANCER DRUGS

To the rescue?

Overexpression of the c-*MYC* proto-oncogene has been documented in a wide range of human cancer types, and so represents a potentially important target for anticancer agents. In a recent paper in *Proceedings of the National Academy of Sciences*, Hurley and colleagues report on a unique mutational mechanism for overexpression of c-*MYC* in human colorectal cancers, and highlight a strategy that might allow the consequences of this mutational event to be reversed — that is, therapeutically rescued.

Previous studies have identified a genetic structure known as a G-quadruplex — a four-guanine stretch of DNA — that functions as a negative regulator of c-*MYC* expression. Furthermore, G-to-A mutations at specific positions within the G-quadruplex destabilize this structure and lead to increased expression of c-*MYC*.

Hurley and colleagues previously reported that the treatment of tumour cell lines with the cationic porphyrin compound TMPyP4, which is able to stabilize the G-quadruplex, leads to a reduction in the levels of c-*MYC* mRNA and protein. Following on from this, the present study looked for G-quadruplex mutations in colorectal cancer specimens, along with surrounding tissue, from 21 patients. Of the 21 samples, 6 were found to carry mutations that are known to disrupt the G-quadruplex of the c-*MYC* promoter; moreover, no G-quadruplex-destabilizing mutations were found in the normal surrounding tissue. No non-transformed cells from the 21 tumour samples carried a mutation that would result in destabilization of the G-quadruplex, nor did 20 colon adenomas — early stages of colorectal cancer — that were examined. Taken together, these findings indicate that the destabilizing mutations are positively selected for in cancer cells during the evolution of tumours, through the effects they have on c-*MYC* expression.

Although it was already known that TMPyP4 could stabilize G-quadruplexes and reduce expression of c-*MYC*, Hurley *et al.* extended this by revealing that in cells with lower levels of NM23-H2 — a protein known to activate c-*MYC* transcription — stabilization by TMPyP4 was enhanced. So, overall, this work suggests a novel potential approach to the modulation of the expression of c-*MYC*, a key gene underlying a range of cancer types, and in particular, the possibility of reversing the consequences of a late mutational event in this gene.

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References and links

ORIGINAL RESEARCH PAPER Grand, C. L. *et al*. Mutations in the G-quadruplex silencer element and their relationship to c-*MYC* overexpression, NM23 repression, and therapeutic rescue. *Proc. Natl Acad. Sci. USA* **101**, 6140–6145 (2004)

FURTHER READING Siddiqui-Jain, A. *et al.* Direct evidence for a G-quadruplex in a promoter region and its targeting with a small molecule to repress c-MYC transcription. *Proc. Natl Acad. Sci. USA* **99**, 11593–11598 (2002)