Refolding mutant p53: a simple way to resolve a complex problem?

In their excellent overview, David Lane and Ted Hupp [1] gave new insights into the folding pathways of cellular proteins, exemplified by p53. They highlighted an innovative therapeutic strategy to restore normal function to mutant p53, or enhance the function of normal p53, by using low-molecular-weight agents and antibodies to effect conformational changes in the p53 molecule. Considering the high frequency of p53 mutations in human malignancies, this model is an appealing approach to the development of new and more cause-specific anticancer drugs.

A crucial prerequisite for successful implementation of the p53-restoring concept in cancer treatment is that downstream effectors of the p53 cascade are not additionally disabled in a p53-null or -mutated context. However, the main data supporting this view rely on genomic analysis of the respective effectors without consideration of possible epigenetic alterations. The latter are all the more important in light of recent findings showing that long-term exclusion of genes from active transcription, as could be the case for a subset of p53-dependent genes during the evolution of p53-deficient tumors, causes promoter hypermethylation. This leads to the subsequent locking of genes into an inactivated chromatin state by the attraction of methylation-binding proteins and histone deacetylation [2,3]. Hence, it is tempting to speculate that, in addition to restoration of p53 DNA-binding ability via refolding strategies, the receptiveness of downstream target promoter regions is crucial for reactivation of the complete p53 tumor suppressor function. The lack of consistent data in this field led us to investigate the occurrence and consequences of aberrant epigenetic events in p53-dependent genes in a p53-mutated cellular context.

However, there is a second, transcription-independent apoptogenic p53 pathway [4]. Recently, Ute Moll and co-workers pointed out that wild-type p53 directly induces mitochondrial permeabilization and cytochrome *c* release, by forming complexes with the anti-apoptotic Bcl-x_L and Bcl-2 proteins [5]. p53 interacts with these factors via its DNA-binding domain making this alternative apoptotic pathway particularly attractive for therapeutic p53-refolding approaches (provided that refolding compounds do not hinder the interactions with these death-protective factors).

Furthermore, it remains to be established whether dominant-negative crosstalk between refolded p53 and splice variants of p53 family members, such as ΔNp73, ΔNp63 and p73-Ex2Del, when overexpressed in cancers, might reduce the effectiveness of drug-induced refolding strategies [6].

Another key point is how the low-molecular-weight agents affect other subsets of molecules in normal cells. For example, over-stabilization of wild-type p53 could be harmful to some cell types such as intestinal epithelium and hematopoietic cells, which are known to be particularly vulnerable to p53-induced cell death.

Putting the tumor suppressor *par excellence* back on duty is one of the most fascinating perspectives in current cancer research. However, clinical trials will be necessary to reveal the true therapeutic power of the agents in question and to disclose unequivocally how far we still are from 'p53-reactivating magic anticancer bullets'.

References

1 Lane, D.P. and Hupp, T.R. (2003) Drug discovery and p53. *Drug Discov. Today* 8, 347–355

2 Song, J.Z. *et al.* (2002) Hypermethylation trigger of the glutathione-S-transferase gene (*GSTP1*) in prostate cancer cells. *Oncogene* 21, 1048–1061

3 Burgers, W.A. *et al.* (2002) DNA methyltransferases get connected to chromatin. *Trends Genet.* 18, 275–277

4 Marchenko, K. *et al.* (2000) Death signal-induced localization of p53 protein to mitochondria. A potential role in apoptotic signaling. *J. Biol. Chem.* 275, 16202–16212

5 Mihara, M. *et al.* (2003) p53 has a direct apoptogenic role at the mitochondria. *Mol. Cell* 11, 577–590

6 Moll, U.M. *et al.* (2001) p53, p63, p73 – solos, alliances and feuds among family members. *Biochim. Biophys. Acta* 1552, 47–59

Alain G. Zeimet
Department of Obstetrics and Gynecology
Innsbruck University Hospital
Anichstrasse 35 , 6020 Innsbruck, Austria

1359-6446/03/$ – see front matter PII: S1359-6446(03)02755-7