© 1995 Nature Publishing Group http://www.nature.com/naturemedicine

trol. For example, the use of pluramycin to freeze TBP–TATA binding complexes appears to offer significant possibilities for examining the assembly of transcriptional complexes. Just as antibiotics were invaluable tools in elucidating the steps in protein synthesis, specific DNA-reactive compounds may be useful probes for unraveling the complexities of transcriptional control.

1. Hurley, L.H. DNA and associated targets for drug design. *J. med. Chem.* **32**, 2027–2033 (1989).
2. Basu, A.K. & Essigmann, J.M. Site-specifically modified oligodeoxynucleotides as probes for the structural and biological effects of DNA-damaging agents. *Chem. Res. Tox.* **1**, 1–18 (1988).
3. MacLeod, M.C., Powell, K.L. & Tran, N. Binding of the transcription factor, Sp1, to non-target sites in DNA modified by benzo[*a*]pyrene diol epoxide. *Carcinogenesis* (in the press).
4. Li, B., Mao, B., Xu, J., Amin, S., Ibanez, V. & Geacintov, N.E. Distortions in stereospecific and site-specific BPDE–DNA adducts. *Proc. Am. Assoc. Cancer Res.* **35**, 111 (1994).
5. Treiber, D.K., Zhai, X., Jantzen, H. & Essigmann, J.M. Cisplatin–DNA adducts are molecular decoys for the ribosomal RNA transcription factor hUBF (human upstream binding factor). *Proc. natn. Acad. Sci. U.S.A.* **91**, 5672–5674 (1994).
6. Brown, S.J., Kellett, P.J. & Lippard, S.J. Ixr1, a yeast protein that binds to platinated DNA and confers sensitivity to cisplatin. *Science* **261**, 603–605 (1993).
7. Sun, D. & Hurley, L.H. Cooperative bending of the 21-base-pair repeats of the SV40 viral early promoter by human Sp1. *Biochemistry* **33**, 9578–9587 (1994).
8. Ho, S.N., Boyer, S.H., Schreiber, S.L., Danishefsky, S.J. & Crabtree, G.R. Specific inhibition of formation of transcription complexes by a calicheamicin oligosaccharide: A paradigm for the development of transcriptional antagonists. *Proc. natn. Acad. Sci. U.S.A.* **91**, 9203–9207 (1994).
9. Walker, S., Murnick, J. & Kahne, D. Structural characterization of a calicheamicin–DNA complex by NMR. *J. Am. Chem. Soc.* **115**, 7954–7961 (1993).
10. Dorn, A., Affolter, M., Muller, M., Gehring, W.J. & Leupin, W. Distamycin-induced inhibition of homeodomain–DNA complexes. *EMBO J.* **11**, 279–286 (1992).
11. Chiang, S., Welch, J., Rauscher, F.J. & Beerman, T.A. Effects of minor groove binding drugs on the interaction of TATA box binding protein and TFIIA with DNA. *Biochemistry* **33**, 7033–7040 (1994).
12. Mitscher, L.A. & Shen, L.L. A cooperative quinolone–DNA binding model for DNA gyrase inhibition. in *Nucleic Acid Targeted Drug Design* (eds Propst, C.L. & Perun, T.J.) 375–421 (Marcel Dekker, Inc., New York, 1992).
13. Potmesil, M. Camptothecins: From bench research to hospital wards. *Cancer Res.* **54**, 1431–1439 (1994).
14. Fan, J.-Y., Sun, D., Yu, H., Kerwin, S. & Hurley, L.H. The self-assembly of a quinobenzoxazine–Mg^{2+} complex on DNA: A new paradigm for the structure of a drug–DNA complex and implications for the structure of the quinolone bacterial gyrase–DNA complex. *J. med. Chem.* **38**, 408–424 (1995).
15. Sun, D. & Hurley, L.H. Demonstration of the asymmetric TBP-induced unwinding of the region immediately downstream of the TATA box using the intercalating DNA-reactive drug pluramycin. *Proc. Am. Assoc. Cancer Res.* **36**, 534 (1995).
16. Adams, E.G., Badiner, G.J. & Bhuyan, B.K. Effects of U-7,184 and several other CC-1065 analogues on cell survival and cell cycle of Chinese hamster ovary cells. *Cancer Res.* **48**, 109–116 (1988).

Drug Dynamics Institute
College of Pharmacy
The University of Texas at Austin
Austin, Texas 78712, USA

Multidrug resistance: Locked in the vault?

LEONARD H. ROME

The discovery that multidrug resistance could be explained by transmembrane transporter molecules (MRP and PgP) acting as pumps to remove toxic drugs was soon followed by the realization that some tumours resisted chemotherapy by an alternate mechanism. The article by Scheffer *et al.* in this issue of *Nature Medicine*[1] sheds new light on this important problem. This group has for some time been focusing on a protein, LRP, found to be overexpressed in non-PgP multidrug resistant tumour cell lines. In addition to its presence in drug-resistant lines, LRP expression was shown to decrease in at least one line that lost the resistant phenotype. It also appears to have a high predictive value for resistance to chemotherapy in acute myeloid leukemia and ovarian carcinoma.The present article, describes the isolation and sequencing of a full-length cDNA encoding LRP; surprisingly it turns out to be the human homologue of the major vault protein. This protein of which the cDNA was previously cloned and sequenced from rat and *Dictyostelium*, is the major structural protein of the vault, a large abundant cytoplasmic ribonucleoprotein particle which has been highly conserved from slime mold to man.

Since vaults were first described nearly ten years ago[2], we have been searching for the function of these organelles. Structural studies reveal the vault to be a large (12.9 megadaltons), ovoid barrel-like particle with dimensions of approximately 35 x 60 nm. A single vault is composed of two eightfold symmetric halves and each half can be shown to open into a delicate eight-petaled flower (see figure, reviewed in 3). This unusual structure led us to examine vaults as possible components of the eightfold symmetric nuclear pore complex (NPC). They are most similar to the central plug of the NPC, which has dimensions, mass and geometry nearly identical to the vault particle. This relationship has been supported by immunolocalization studies which demonstrate that vaults can associate with nuclear membranes and NPCs[4]. If vaults are NPC plugs, their abundance and cellular distribution suggests that they may function in nucleo-cytoplasmic transport. Vaults contain multiple copies of a single small RNA (vRNA) with a conserved secondary structure[5], making it tempting to speculate that the transport cargo of vaults is cellular RNA, which associates with vaults via an interaction with the vRNA.

A model of vault structure. Intact vaults unfold into a dual flower conformation. Reproduced with permission.

The evidence linking vaults and the multidrug resistance phenotype is still circumstantial. Resistance does not appear to be due solely to over expression of the major vault protein and may require the intact vault particle. A definitive role for vaults in multidrug resistance will require a direct demonstration that vault expression can confer resistance on cells and that specific interference with vaults in non-PgP multidrug resistant cell lines restores drug sensitivity. For now, however, the prospect that vaults could play a role in mediating multidrug resistance opens new avenues for functional studies, and the exciting possibility that anti-vault therapeutic reagents could be designed to lower the resistance of tumours to drug treatment.

1. Scheffer, G.L. *et al.* The drug resistance-related protein LRP is the human major vault protein. *Nature Med.* **1**, 578–582 (1995).
2. Kedersha, N.L. & Rome, L.H. Isolation and characterization of a novel ribonucleoprotein particle: Large structures contain a single species of small RNA. *J. Cell Biol.* **103**, 699–709 (1986).
3. Rome, L., Kedersha, N. & Chugani, D. Unlocking vaults: Organelles in search of a function. *Trends Cell Biol* **1**, 47–50 (1991).
4. Chugani, D.C., Rome, L.H. & Kedersha, N.L. Localization of vault particles to the nuclear pore complex. *J. Cell Sci.* **106**, 23–29 (1993).
5. Kickhoefer, V.A. *et al.* Vault RNP particles from rat and bullfrog contain a related small RNA that is transcribed by RNA polymerase III. *J. biol. Chem.* **268**, 7868–78173 (1993).

Department of Biological Chemistry
UCLA School of Medicine
Los Angeles, California 90024, USA