

## CRYSTAL STRUCTURE OF MURINE TCL1 ONCOPROTEIN AND CONSERVED SURFACE FEATURES OF THE MOLECULES OF THE TCL1 FAMILY

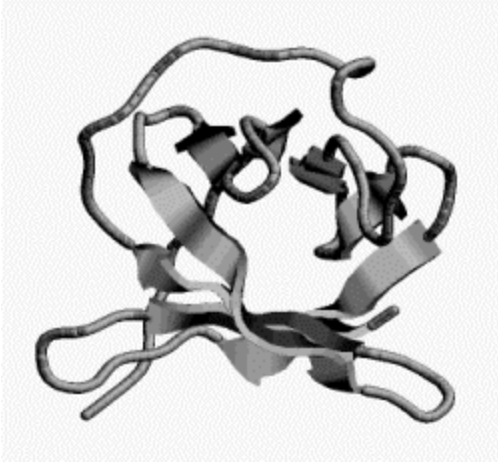
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**INTRODUCTION.** The structures of members of the Tc11 oncoprotein family are being studied in order to understand their roles in lymphocyte biology and their development of lymphocytic diseases[1-3]. These ~15 kD proteins share 25–80% sequence identity between the members of the family. No sequence similarity was found with other human genes suggesting a unique cellular role(s). Family members share an uncommon tertiary structure of an eight-stranded beta barrel. Recently, the crystal structure of murine Tc11 was determined[3]. The three structures were analyzed to reveal conserved features indicative of a potential binding site for an interacting protein.

**METHODS.** Murine Tc11 crystals were prepared as described[3]. X-ray diffraction data were collected on a Quantum 4 detector at beamline X12B of the National Synchrotron Light Source at Brookhaven National Laboratories. The structure was solved using a homology model based on the human Tc11 structure. The crystals showed pseudo-merohedral twinning that generated a pseudo-*I*222 symmetry. Therefore, the structure was refined with SHELX97 to handle crystal twinning[4].

**RESULTS.** The mTc11 structure consists of a dimer in the C2 space group with  $R = 0.226$ ,  $R$ -free = 0.236. The crystal structures of mTc11, hTc11, and hMtcp1 are very similar (Fig. 1). Human and murine Tc11 have an RMSD of ~0.6 Å for 100 C $\alpha$  atoms, while murine Tc11 and human Mtcp1 show ~0.5 Å RMSD for 97 C $\alpha$  atoms. The three protein structures have high internal symmetry from a tandem repeat with RMSD ranging from 1.1–1.7 Å despite low sequence identity of 12–13%. All three structures share a conserved planar surface that may be involved in protein-protein interactions.



**FIGURE 1.**

**DISCUSSION.** Tc11, Tc11b, and Mtcp1 were shown to interact with the protein kinase Akt, which plays a key role in proliferation and survival of lymphocytes[5]. Comparison of the structures has defined common regions as potential binding sites for interacting proteins that modulate the cellular function of these unique oncoproteins. The Tc11 family share very similar tertiary structures with a common planar surface. However, the planar surfaces of Tc11 and Mtcp1 differ in the charge distribution, suggesting that they do not bind the same protein or bind it in different orientations.

**ACKNOWLEDGMENTS.** Many thanks to Dr. B. Mahalingam, Dr. G. Sheldrick, and Dr. R. Herbst-Irmer. This work was supported by the Elsa U. Pardee Foundation and the National Cancer Institute grant CA76259.

#### **REFERENCES**

1. Fu, Z.Q., Du Bois, G.C., Song, S.P., Kulikovskaya, I., Virigilio, L., Croce, C.M., Weber, I.T., and Harrison, R.W. (1998) *Proc. Natl. Acad. Sci. U. S. A.* 95, 3413–3418.
2. Hoh, F., Yang, Y.S., Guignard, L., Padilla, A., Stern, M.H., Lhoste, J.M., and van Tilbeurgh, H. (1998) *Structure* 6, 147–155.
3. Petock, J.M., Torshin, I.Y., Wang, Y.F., Dubois, G.C., Croce, C.M., Harrison, R.W., and Weber, I.T. (2001) *Acta Crystallogr. D* 57, 1545–1551.
4. Herbst-Irmer, R. and Sheldrick, G.M. (1998) *Acta Crystallogr. B* 54, 443–449.
5. Pekarsky, Y., Koval, A., Hallas, C., Bichi, R., Tresini, M., Malstrom, S., Russo, G., Tschlis, P., and Croce, C.M. (2000) *Proc. Natl. Acad. Sci. U. S. A.* 97, 3028–3033.