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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 Tcl1 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 Tcl1 was determined[3]. The three structures were analyzed to reveal conserved features indicative of a potential binding site for an interacting protein.

METHODS. Murine Tcl1 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 Tcl1 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 mTcl1 structure consists of a dimer in the C2 space group with $R = 0.226$, R-free = 0.236. The crystal structures of mTcl1, hTcl1, and hMtcp1 are very similar (Fig. 1). Human and murine Tcl1 have an RMSD of ~0.6 Å for 100 Cα atoms, while murine Tcl1 and human Mtcp1 show ~0.5 Å RMSD for 97 Cα 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.

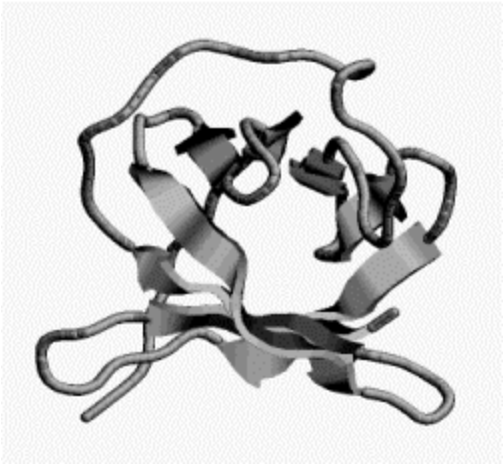

FIGURE 1.

DISCUSSION. Tcl1, Tcl1b, 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 Tcl1 family share very similar tertiary structures with a common planar surface. However, the planar surfaces of Tcl1 and Mtcp1 differ in the charge distribution, suggesting that they do not bind the same protein or bind it in different orientations.

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