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Structural Basis for Inhibition of Translation by the Tumor Suppressor, Pcd4. Nicole LaRonde-LeBlanc¹, Arti Santhanam², Nancy H. Colburn², Alexander Wlodawer¹, ¹Macromolecular Crystallography Laboratory and ²Laboratory of Cancer Prevention, Center for Cancer Research, NCI, Frederick, MD 21702.

The tumor suppressor Programmed Cell Death 4 (*Pcd4*) inhibits the translation of mRNA with complex 5' untranslated regions through interactions with components of the translation initiation complex, eIF4F, in particular the RNA helicase eIF4A. These interactions occur through two MA3 domains in the Pcd4 molecule. We have determined the structure of the C-terminal MA3 domain of Pcd4 (cMA3) at 2.0 Å resolution. The crystals, which belong to space group P3₁21 with 2 molecules per asymmetric unit, exhibit an unusual form of disorder. The final 2F_o-F_c electron density was excellent for molecule A, but considerably poorer for molecule B. Several scenarios were explored to explain this anomaly, but so far none was able to do so. Using the unquestionably correct structure of molecule A, we demonstrate that the cMA3 domain of Pcd4 shows remarkable structural similarity to an MA3 domain located near the C-terminus of eIF4G (eIF4Gc). We show that the cMA3 domain of Pcd4 competes with eIF4Gc for binding to eIF4A and that this MA3 domain alone is sufficient for inhibition of translation. This work provides a clear structural explanation for inhibition of eIF4A-mediated translation by Pcd4.