Scientists Reveal Details of Calcium Safety-Valve in Cells

Scientific Achievement

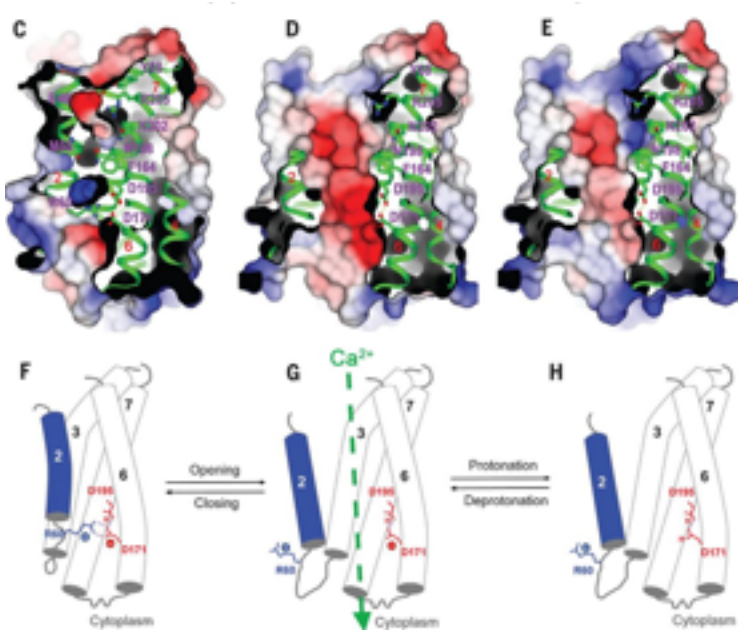
Deciphered the atomic level structure of a protein that regulates the level of calcium in cells, a key signaling agent that can trigger programmed cell death

Significance and Impact

Understanding what happens when programmed cell death goes awry could help scientists identify new targets for anticancer drugs.

Research Details

- Studied prokaryotic homolog of human "Transmembrane Bax Inhibitor Motif" (TMBIM) proteins, which come in six varieties. TMBIM6 is overexpressed in various cancers, including prostate, breast, glioma, uterine, ovarian, lung.
- Atomic-level structures were determined using x-ray crystallography at NSLS beamlines X4A and X4C.
- Images of the protein reveal a novel structure consisting of a centralized helix wrapped by two novel triple-helix sandwiches that traverse the membrane. The central portion can be open or closed, depending on the acidity level (pH). At physiological pH, open and closed conformations exist in equilibrium, maintaining a steady state of calcium in the cell by allowing gradual leakage of calcium across the membrane through a transmembrane pore.



Structural and functional characterization of calcium leak: C) electrostatic surface of closed-conformation structure showing charged surface concavities and internal cavities but a blocked pore; D) electrostatic surface of open-conformation structure at pH 7.4, where cleft is electronegative; E) electrostatic surface for open-conformation structure at Ph6, where cleft is more neutral. Red is negative potential, blue is positive potential. F-H) Proposed model for pH-sensitive calcium leak.

Y. Chang, R. Bruni, B. Kloss, Z. Assur, E. Kloppmann, B. Rost, W. A. Hendrickson, Q. Liu. *Science*, **v. 344, no. 6188** pp. 1131-1135 (2014)

Work was performed at Brookhaven National Laboratory