Zn2+-binding and Molecular Determinants of Tetramerization in Voltage-gated K+ Channels

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The N-terminal, cytoplasmic tetramerization domain (T1) of voltage-gated potassium channels encodes molecular determinants for subfamily-specific assembly of alpha-subunits into functional tetrameric channels. Here we present crystal structures of T1 tetramers from Shaw and Shaker subfamilies in order to elucidate differentiating determinants at the subunit interfaces. The structures reveal a C-terminal layer (designated layer 4) on the hypothetical membrane-facing side of the previously determined structure of Shaker T1 domain (layers 1 - 3).[1] Within this layer, the Shaw T1 tetramer contains four zinc ions; each is coordinated by a histidine and two cysteines from one monomer and by one cysteine from an adjacent monomer. The presence of zinc in the Shaw T1 crystals was verified by XAS. Anomalous difference Patterson maps calculated with x-ray data collected at the zinc K edge (1.28 Å) independently verified the position of the zinc ion within the monomer. The amino acids involved in coordinating the zinc ion occur in a HX5CX20CC sequence motif, which is highly conserved among Shab, Shaw, and Shal subfamily members but is not found in Shaker subfamily members. The high sequence conservation of this motif suggests an important structural role for zinc coordination in non-Shaker type K+ channels.

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[1]Kreusch, A., et al. "Crystal Structure of the Tetramerization Domain of the Shaker Potassium Channel." Nature 392, 945-948 (1998).