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FOR THE RECORD

Presenilin adopts the ClC channel fold

Douglas L. Theobald*

Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02453

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Abstract: Presenilin is an integral membrane aspartate protease that regulates cellular processes by cleaving proteins within the cell membrane. The recent crystal structure of presenilin reveals a conspicuous pore in a bundle of nine α-helices, which was originally thought to adopt a novel protein fold. However, here I show that the presenilin fold is a variant of the ClC chloride channel/transporter fold. This observation may have important implications for presenilin's postulated biological role as a calcium leak channel.

Keywords: presenilin; ClC channel; protein fold; calcium leak channel

Introduction

Presenilin and signal peptide peptidase are representatives of a family of eukaryotic intramembrane aspartyl proteases that regulate various biological functions via proteolysis of membrane-embedded proteins.[1,2] Presenilin is the catalytic component of γ-secretase, which cleaves amyloid precursor protein leading to formation of amyloid brain plaques seen in patients with Alzheimer's disease. The structure of an archaeal presenilin/signal peptide peptidase homolog (PSH) reveals a homotetramer, with each subunit composed of nine transmembrane α-helices [Fig. 1(a)].[3,4] While preliminary homology searches using DALI failed to find extensive structural similarities with any other known proteins,[3,5] the PSH monomer in fact adopts a fold similar to the seven-helix fold of the ClC chloride channel family [Fig. 1(b)].[6]

*Correspondence to: Douglas L. Theobald, Department of Biochemistry, Brandeis University, Waltham, MA 02453.
E-mail: dtheobald@brandeis.edu

Results

ClC-type chloride channels and transporters enable the selective flow of chloride ions across cell membranes and control diverse physiological processes in both eukaryotes and bacteria. ClCs are "double-barrelled" homodimers, where each monomer comprises two tandem, anti-parallel domains adopting the same fold (hereafter called the ClC fold, see rainbow colored helices in Figure 1(b).[6]

The ClC fold can be described as a bundle of seven α-helices [Figs. 1(b) and 2(a)]. When the ClC fold is viewed perpendicular to the plane of the membrane (starting with the N-terminus on the side of the viewer), the N-terminal helix A packs on one side of the bundle, helix B crosses to the opposite side, followed by helices C, D, E, and F in a roughly counter-clockwise manner around helix B, finishing with helix G reaching back to pack with helices A and E. As can be seen from the secondary structure representations in Figure 1, the PSH fold also adopts this particular fold architecture, allowing for apparent "looser" helical packing, variation in detail of inter-helical contacts, and differences in helical angle relative to the membrane. The PSH domain is further decorated at the very C-terminus with two additional helices not found in ClCs [light mauve in

Fig. 1(a)]. The topological similarity between the PSH and ClC domains is emphasized by contrasting with the only other seven-helix transmembrane fold known, the GPCR fold [Fig. 2(b)], which adopts a radically different architecture and helical connectivity.

Intriguingly, in both PSH and ClC, the same side of the fold participates in protein–protein interactions with other domains in the multimer: in ClCs, helices B, C, and F interact with the other anti-parallel repeat, whereas in PSH the corresponding helices participate in the tetramer interface. Furthermore, the general location of the PSH transmembrane "hole" largely coincides with the chloride permeation pathway in ClCs. The biological significance of the PSH hole is currently unknown, but it is intriguing that presenilin has been reported to have calcium ion channel activity[7,8] and to play a role in regulation of intracellular calcium homeostasis[9,10] (for discussion, see Ref. 11). Several mutations that purportedly affect calcium leak activity[12] line the presenilin "hole" [particularly those in helices F and G, orange and red, respectively, in Fig. 1(a)], while others do not [primarily mutations mapping to helix 9, which is mauve in Fig. 1(a)]. From these findings and others[13] it has been postulated that

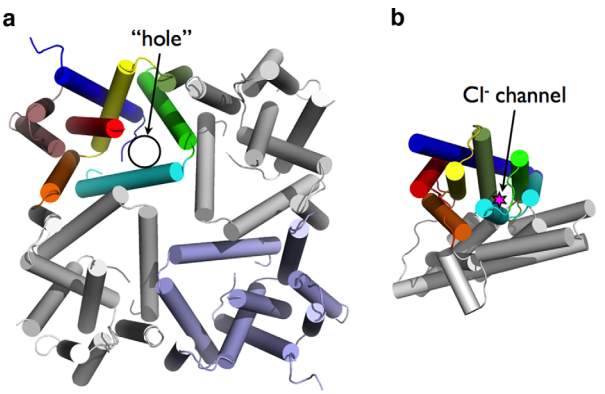

Figure 1. Secondary structure cartoons of PSH and ClC proteins. The protein chains are colored blue to red proceeding from the N-terminus to the C-terminus. The view is perpendicular to the plane of the membrane, looking "down" the helices, with the N-terminus of the first helix (helix A, blue) facing the viewer. Note that in both proteins the polarity of the corresponding α-helices is identical, e.g., the N-terminus of the yellow helix E is pointing toward the viewer. (a) PSH tetramer (PDB ID: 4HYG). Only chain A (one of the monomers) is shown in rainbow colors; the remaining three subunits are white and light blue. (b) *Escherichia coli* ClC chloride channel (PDB ID: 1OTS). The first internal tandem domain is shown in rainbow colors, while the second internal tandem domain, oriented antiparallel to the first, is colored grey. A pink star indicates the general location of bound chloride. In this representation, ClC helix B is considered a single transmembrane helix interrupted by a short transverse loop; in Ref. 6 this helix is represented as two stacked helices, neither of which fully crosses the membrane.

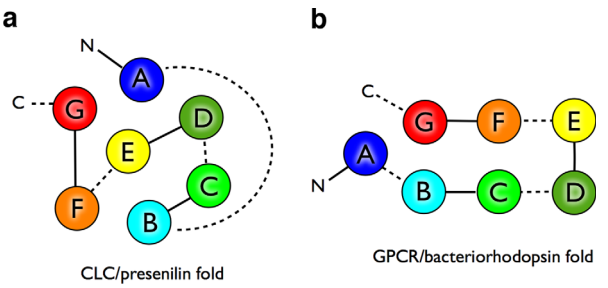

Figure 2. Schematic representation of the seven-helix ClC and GPCR folds. Helices are shown as circles, in an idealized view analogous to Figure 1, looking "down" the helices and perpendicular to the plane of the membrane. The protein chains are colored blue to red proceeding from the N-terminus to the C-terminus, with the seven successive α-helices lettered from A to G. Solid lines represent interhelical loops on the viewer side of the membrane; dashed lines represent interhelical loops on the opposite, far side of the membrane. (a) The ClC/PSH fold. (b) The GPCR/bacteriorhodopsin fold.

presenilin is implicated in the calcium misregulation seen in Alzheimer's disease,[7,14] though this hypothesis is currently controversial.[15,16] The fundamental architectural similarities between presenilin and ClCs may therefore have important implications for understanding the presenilin function, including its possible physiological role as a calcium channel.

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