Transmembrane topology of human erythrocyte anion exchanger 1 protein observed by combined transmembrane topology and the signal peptide predictor method

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Μελέτη της διαμεμβρανικής τοπολογίας της πρωτεΐνης ανταλλαγής ανιόντων-1 των ανθρώπινων ερυθροκυττάρων με συνδυασμένη πρόβλεψη διαμεμβρανικής στερεοδομής και ανάλυσης πεπτιδίων σήμανσης

Περίληψη στο τέλος του άρθρου

Key words: Human erythrocyte anion exchanger 1 protein, Topology, Transmembrane

In physiological circumstances, erythrocyte aging leads to binding of autologous IgG, followed by recognition and removal through phagocytosis, mainly by Kupffer cells in the liver.[1] This process is triggered by the appearance of a senescent erythrocyte-specific antigen.[1] Human erythrocyte anion exchanger 1 protein or band 3 is an important protein related to erythrocyte aging. Red band 3 blood cells play an important role in the system and provide an ideal vehicle for delivering oxygen to tissues, depending on their metabolic activity.[2] CO_2 is not simply waste matter from tissues, but regulates the amount of oxygen delivered to the tissues from red blood cells, utilizing the synergistic effects of hemoglobin, carbonic anhydrase and the anion exchange activity of band 3 protein.[3] Band 3 modifications that normally occur during physiological red blood cell senescence in humans, and occasionally in pathological conditions, are described in the context of their role in enhancing red blood cell recognition and phagocytic removal.[3] Band 3 modifications are due mostly to oxidative insults that either accumulate gradually during the red blood cell lifespan or impact massively in a shorter time period under pathological conditions.[3] Amino acid substitutions in the membrane domain of band 3 are associated with hereditary stomatocytosis, a red cell condition in which the cells leak sodium and potassium ions.[4] These substitutions appear to convert band 3 from an anion exchanger into a cation channel.[4]

Defects in the structure of band 3 proteins are believed to be an important factor contributing to many red blood cell defects. In ovalocytosis, the Southeast Asian ovalocytosis deletion is likely to cause a pulling-in of the polar amino acid sequence immediately N-terminal to the deletion into the lipid bilayer.[5] Cheung and Reithmeier observed that the Southeast Asian ovalocytosis deletion disrupts the effective integration of transmembrane proteins, probably leaving the region exposed to cytosol.[6] However, knowledge about the structure of this protein is limited. This study was conducted to determine the transmembrane region and orientation of band 3.

MATERIAL AND METHOD

Firstly, the sequence of the human erythrocyte anion exchanger 1 protein was sourced from the database, PubMed. The tool name Phobius was then used for study of the transmembrane region and orientation of human erythrocyte anion exchanger 1 protein. Basically, Phobius is a predictor based on a hidden Markov model (HMM) that models the different sequence regions of a signal peptide and the different regions of a transmembrane protein in a series of interconnected states.[7]

RESULTS

The sequence of human erythrocyte anion exchanger 1 protein was derived (P02730) as shown in figure 1. The transmembrane topology pattern is shown in figure 2. Twelve transmembrane regions can be seen at 405–428, 449–471, 491–516, 523–545, 565–584, 604–624, 661–680, 701–724, 761–780, 787–811, 831–850, 857–878.

COMMENT

Transmembrane proteins are an important class of proteins involved in many diverse biological functions, many of which have significant impact in terms of disease mechanism and drug discovery.[8] Despite their biological importance, it has proved very difficult to solve the structures of these proteins by experimental techniques, and

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1 meelqddyed mmeenleqee yedpdipesq meepaahdte atatdyhtts hpgthkvyve

61 lqelvmdekn qelrwmeaar wvqleenlge ngawgrphls hltfwsllel rrvftkgtvl

121 ldlqetslag vanqlldrfi fedqirpqdr eellralllk hshageleal ggvkpavltr

181 sgdpsqpllp qhssletqlf ceqgdggteg hspsgileki ppdseatlvl vgradfleqp

241 vlgfvrlqea aeleavelpv pirflfvllg peaphidytq lgraaatlms ervfridaym

301 aqsrgellhs legfldcslv lpptdapseq allslvpvqr ellrrryqss pakpdssfyk

361 gldlnggpdd plqqtgqlfg glvrdirrry pyylsditda fspqvlaavi fiyfaalspa

421 itfggllgek trnqmgvsel listavqgil fallgaqpll vvgfsgpllv feeaffsfce

481 tngleyivgr vwigfwlill vvlvvafegs flvrfisryt qeifsflisl ifiyetfskl

541 ikifqdhplq ktynynvlmv pkpqgplpnt allslvlmag tfffammlrk fknssyfpgk

601 lrrvigdfgv pisilimvlv dffiqdtytq klsvpdgfkv snssargwvi hplglrsefp

661 iwmmfasalp allvfilifl esqittlivs kperkmvkgs gfhldlllvv gmggvaalfg

721 mpwlsattvr svthanaltv mgkastpgaa aqiqevkeqr isgllvavlv glsilmepil

781 sriplavlfg iflymgvtsl sgiqlfdril llfkppkyhp dvpyvkrvkt wrmhlftgiq

841 iiclavlwvv kstpaslalp fvliltvplr rvllplifrn velqcldadd akatfdeeeg

901 rdeydevampv

Figure 1. Sequences of hepatitis B envelope proteins.

there has been a great deal of pressure to develop effective methods for predicting their structure.[8] Basically, band 3 proteins, members of the anion exchange family of proteins, are involved in a number of physiological activities such as cell volume and osmotic homeostasis, HCO^-_3/Cl^- exchange, red cell aging, IgG binding and cellular removal, and the maintenance of the structural integrity of cells. They are present in the membranes of all cells and cellular organelles examined including Golgi, mitochondria and nuclei.[9] Band 3 disorders can be seen in many red blood cell diseases.[9]

In this work, the transmembrane human erythrocyte anion exchanger 1 protein was studied. Although there was a previous report on the transmembrane structure of band 3, it did not explore overall topology of this protein.[10,11] Groves and Tanner proposed that there might be about 11–12 spans within band 3.[12] According to this study, 12 spans can be seen. The study used the advanced protein topology technique to study band 3, a technique which ranks among the most accurate methods in computational biology.[8] The topology pattern of the protein derived according to this study can be useful for the future study of the pathogenesis of red blood cell membrane defects.

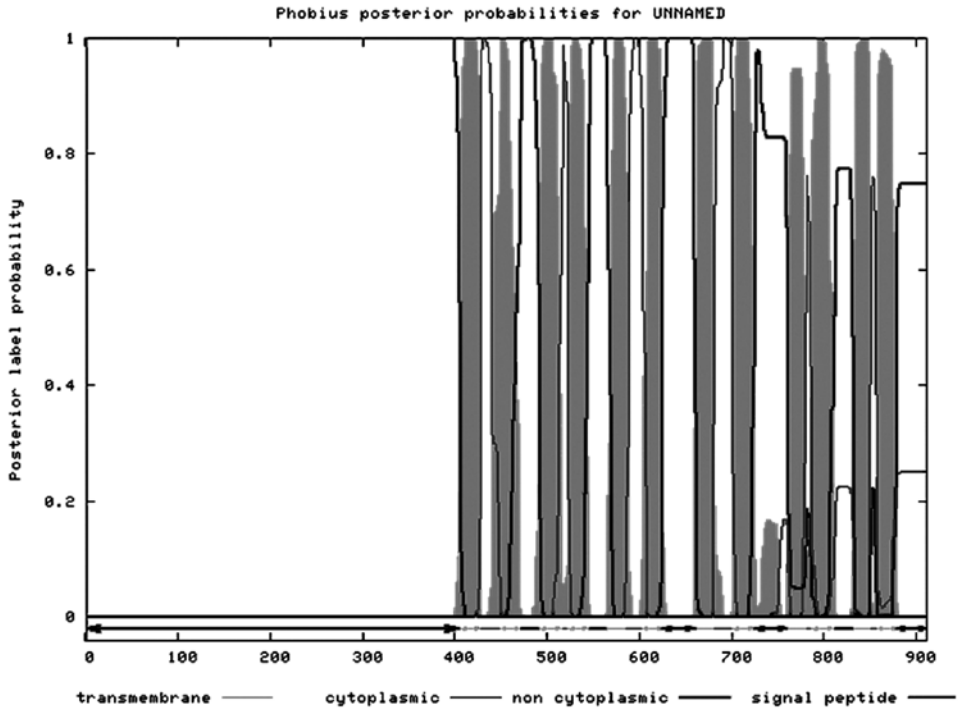

Figure 2. The transmembrane topology pattern of human erythrocyte anion exchanger 1 protein.

ΠΕΡΙΛΗΨΗ

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Η πρωτεΐνη 1 ανταλλαγής ανιόντων ή ταινία 3 των ερυθρών αιμοσφαιρίων του ανθρώπου είναι μια σημαντική πρωτεΐνη, που σχετίζεται με την ηλικία τους. Διαταραχές στην κατασκευή της θεωρείται ότι αποτελούν σημαντικό παράγοντα που συμμετέχει στις διάφορες ανωμαλίες τους. Οι γνώσεις μας για την τοπολογία αυτής της πρωτεΐνης είναι περιορισμένες. Έγινε μελέτη για τον καθορισμό της τοπολογίας της πρωτεΐνης 1 ανταλλαγής ανιόντων. Μπορεί να διακριθούν 12 διαμεμβρανικές περιοχές: 405–428, 449–471, 491–516, 523–545, 565–584, 604–624, 661–680, 701–724, 761–780, 787–811, 831–850, 857–878. Σύμφωνα με τη μελέτη, καθορίστηκε η τοπολογία της πρωτεΐνης 1 ανταλλαγής ανιόντων των ερυθρών. Αυτή η κατανομή μπορεί να είναι χρήσιμη για τη μελέτη των διαταραχών της ερυθροκυτταρικής μεμβράνης.

Λέξεις ευρετηρίου: Διαμεμβρανική πρωτεΐνη, Ερυθροκύτταρο, Πρωτεΐνη ανταλλαγής ανιόντων, Τοπολογία

References

1. BOSMAN GJ, WILLEKENS FL, WERRE JM. Erythrocyte aging: A more than superficial resemblance to apoptosis? *Cell Physiol Biochem* 2005, 16:1–8
2. HAMASAKI N. Band 3 protein as a metabolic sensor – CO_2 regulates the amount of oxygen delivered to tissues from red blood cells. *Rinsho Byori* 2006, 54:263–269
3. ARESE P, TURRINI F, SCHWARZER E. Band 3: Complement-mediated recognition and removal of normally senescent and pathological human erythrocytes. *Cell Physiol Biochem* 2005, 16:133–146
4. BRUCE L. Mutations in band 3 and cation leaky red cells. *Blood Cells Mol Dis* 2006, 36:331–336
5. CHEUNG JC, REITHMEIER RA. Membrane integration and topology of the first transmembrane segment in normal and Southeast Asian ovalocytosis human erythrocyte anion exchanger 1. *Mol Membr Biol* 2005, 22:203–214
6. CHEUNG JC, LI J, REITHMEIER RA. Topology of transmembrane segments 1–4 in the human chloride/bicarbonate anion exchanger 1 (AE1) by scanning N-glycosylation mutagenesis. *Biochem J* 2005, 390:137–144
7. HURWITZ N, PELLEGRINI-CALACE M, JONES DT. Towards genome-scale structure prediction for transmembrane proteins. *Philos Trans R Soc Lond B Biol Sci* 2006, 361:465–475
8. PUNTA M, FORREST LR, BIGELOW H, KERNYTSKY A, LIU J, ROST B. Membrane protein prediction methods. *Methods* 2007, 41:460–474
9. KAY MM. Band 3 and its alterations in health and disease. *Cell Mol Biol* 2004, 50:117–138
10. OTA K, SAKAGUCHI M, HAMASAKI N, MIHARA K. Assessment of topogenic functions of anticipated transmembrane segments of human band 3. *J Biol Chem* 1998, 273:28286–28291
11. TANG XB, FUJINAGA J, KOPITO R, CASEY JR. Topology of the region surrounding Glu681 of human AE1 protein, the erythrocyte anion exchanger. *J Biol Chem* 1998, 273:22545–22553
12. GROVES JD, TANNER MJ. Topology studies with biosynthetic fragments identify interacting transmembrane regions of the human red-cell anion exchanger (band 3; AE1). *Biochem J* 1999, 344:687–697

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