Molecular dynamics of Immunoglobulin transmembrane helix dimerization

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Motivation

The B cell receptor (BCR) is responsible for the first step of immune response mechanisms by specifically recognising different antigens. BCR consists of one membrane-bound immunoglobulin (Ig) molecule, comprising two heavy and two light chains linked by disulfide bridges, associated with the transducing molecular partner, the heterodimer CD79a/CD79b. The region_ of Ig traversing the lipid bilayer (IgTM) is highly conserved among species. It contains a universal sequential motif (CART motif), which is known to be crucial for BCR assembly, since the receptor functionality is abolished when CART residues are substituted by mutagenesis. We investigated the association of the two IgTM regions in the BCR of Chionodraco hamatus (family Channichthyidae), which represents the model species we have chosen for studying immunity in Antarctic teleosts.

Methods

The used methods include nucleotide sequencing of the C. hamatus H chain transcripts, computational analysis to predict the topology of the TM region; homology modelling to build molecular models, and molecular dynamics to study the association and stability of IgTM region dimer structures.

Results

The nucleotide sequence of both the entire C. hamatus membrane-bound and secreted IgH chain was determined by sequencing cDNA clones obtained by cloning RT-PCR products.

Based on alignment of the cDNA sequences coding for the secreted and membrane-bound Ig forms, the primary transcript was shown to undergo alternative splicing patterns in this species. The exons specific for the membrane-bound form were also identified.

Using different computational methods, the length and the polarity of the a-helical region within the cell membrane were predicted. A molecular model of the C. hamatus IgTM region was built: Prosite database was searched using the 3D-PSSM tool, and the helix H of the photosynthetic reaction centre of Rhodobacter sphaeroides was selected as template. The stability of the model was investigated by molecular dynamics (MD) simulations. Models of a TM homodimer were also obtained by performing MD simulations using two copies of the helix, at a 14-16 ï¿½distance between the centres of mass and in different orientations, as starting model. The results of the simulations reveal that two slighlty different conformations (A and B) of a stable dimer can be obtained. In the A conformation, one helix of the dimer was shifted of about 6 ï¿½with respect to the same helix in the conformation B. Finally, the obtained structures were related to the available experimental data collected on IgM TM region of different species.

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