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# Molecular simulations reveal the dynamics of the band 3 anion transporter in a model native red blood cell membrane

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Band 3, the red blood cell anion exchanger (AE1/SLC4A1), is responsible for the rapid transport of bicarbonate and chloride across the red blood cell plasma membrane, a process necessary for efficient respiration. Human Band 3 is comprised of a cytosolic domain and a membrane domain that contains 14 transmembrane helices. Although structural data are available for both isolated domains, the structure of the complete Band 3 remains elusive. This is a limiting factor in the study of Band 3 anion transport and of its interactions with cytosolic proteins. By integrating molecular modelling and molecular dynamics simulations at the coarse-grained and all-atom resolutions, we have constructed a model of Band 3 that consists of both the transmembrane and the cytosolic domains. This model enabled us to identify the orientation of the cytosolic domain relative to the transmembrane domain and the role of the linker regions that connect these two domains in their interactions. Our model was validated using functional data and molecular simulations. Simulations were performed in complex bilayers that resemble the native red cell plasma membrane, containing a full complement of phospholipids, sphingomyelin and cholesterol. Our results provide novel molecular insights into the interactions of the lipid environment with Band 3. Specific lipids, e.g. cholesterol, have been found to localize in the Band 3 dimer interface possibly stabilizing the dimer. Specific lipid head groups were also found to interact with the cytosolic domain regulating its orientation relative to the transmembrane domain. Moreover, our modeling approach identified key residues involved in anion binding. Understanding the dynamics and interactions of Band 3 in a model native red cell membrane provides new insights into the function of this important human transporter.