

Human membrane proteins strike evolutionary balance

May 26 2022

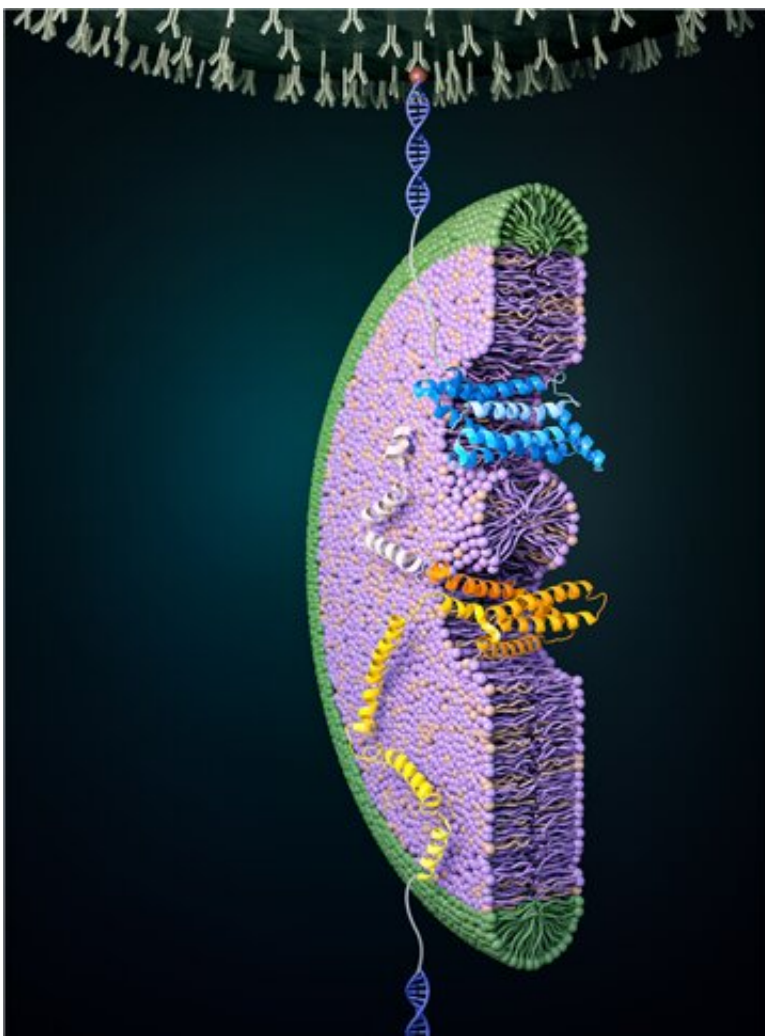


Figure 1: The folding process of a glucose transporter using magnetic tweezers. A high force is applied first to unwind the protein completely. The applied force is then lowered which allows the folding process to be observed. In the picture, a portion of the glucose transporter can be seen being folded to form a structure and enter the bicelle (colored blue). This folding process does not often occur

without external assistance, so this process is accomplished with the help of the surrounding membrane environment and protein complexes such as the EMC. Credit: Seoul National University

Cells are compartmentalized by membranes, and proteins present in these membranes play an important role in transporting cellular information. For proper function of these proteins to occur, a tertiary protein structure must be formed through the correct folding process. In a study published in *Nature Chemical Biology*, the folding process of a glucose transporter—a complex membrane protein—was identified for the first time using single-molecule magnetic tweezers.

Using the [endoplasmic reticulum](#) (ER) membrane [protein](#) complex (EMC) and a lipid molecule with a specific structure, the folding pathway of a glucose transporter was fully elucidated in a physiological environment. Through bioinformatics, it was also discovered that the membrane protein's structure-forming ability and its capacity to transport glucose had to have struck a balance throughout its evolutionary history.

Although the structures of many membrane proteins—including glucose transporters—have already been revealed through recent advances in [structural biology](#) such as cryo-electron microscopy, the folding pathway in which the structures of these membrane proteins is formed remains almost completely unknown. Back in 2019, the research team reported in *Science* that the folding pathways of membrane proteins can be revealed using magnetic tweezers, marking the first time in the world that the folding pathway of a membrane protein was revealed.

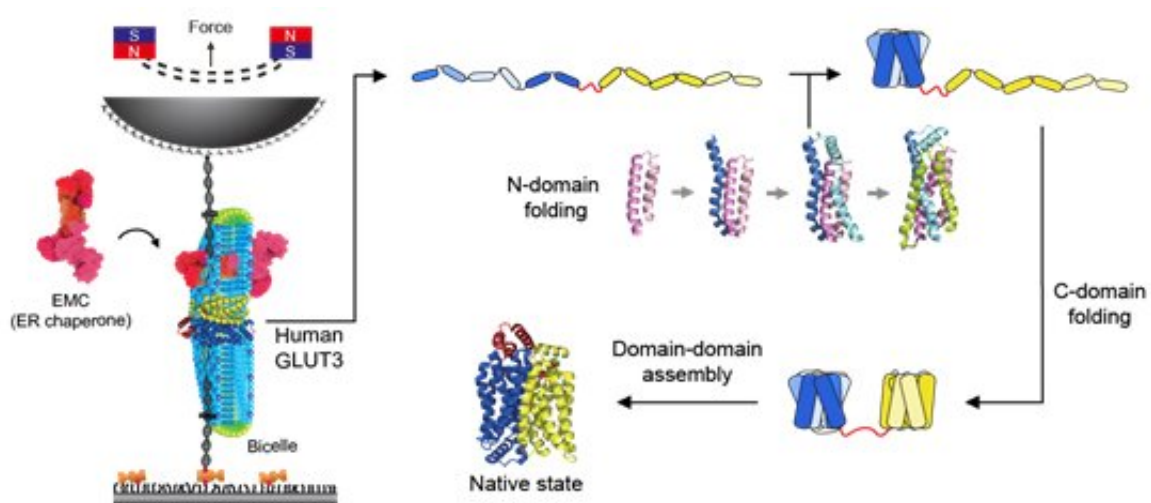


Figure 2: Schematic diagram of magnetic tweezers and the folding pathway of a glucose transporter. The left shows the application of force to the glucose transporter using magnetic tweezers. Bicelles composed of various lipid molecules were supplied to provide an environment required for membrane proteins to function. In addition, EMCs were added to help form the correct tertiary protein structure. When the magnetic bead is pulled toward the permanent magnet, tension is applied to the DNA string connected to the protein, and a constant force is applied to the protein itself. Through this experiment, the folding pathway of the glucose transporter was revealed as shown on the right side of the figure. In the fully unfolded state of individual helix proteins, the N-domain close to the N-terminus is first folded to obtain the protein's structure-forming ability. Then, with the help of the EMC and a uniquely-shaped lipid molecule, the C-domain folds and finally the two domains combine to form a functional tertiary protein structure. Credit: Seoul National University

Magnetic tweezers can be used to apply force to a single protein, thereby completely unfolding a protein's structure. In addition, if the applied force is then lowered, it is possible to observe the process of the released protein refolding back into its original folded shape (Figure 1,2).

Glucose transporter proteins, as the name suggests, are a group of

proteins that possess a pathway through which glucose can pass. Glucose transport pathways are functionally essential, but these pathways also act as obstacles in forming the tertiary structures of membrane proteins. Cells have various helpers to solve these difficulties. In this study, it was found that the EMC—a type of protein chaperone—as well as uniquely-structured lipid molecules work in conjunction in helping the glucose transporter in its structure formation.

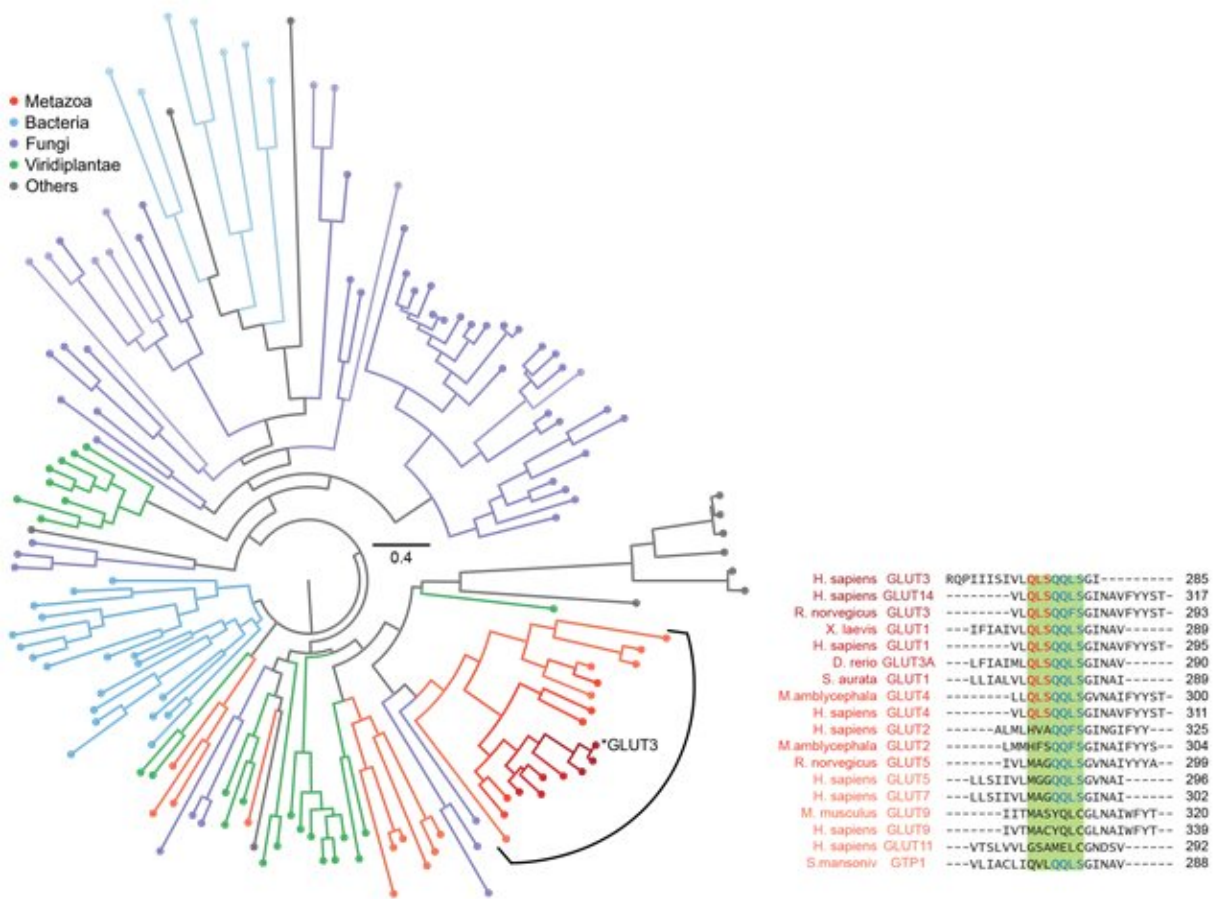


Figure 3: Phylogenetic analysis for various sugar transporters. Bioinformatics was used to analyze the sequence of GLUT3 as well as other evolutionarily-related sugar transport proteins. A total of 143 proteins were analyzed and presented as a phylogenetic tree as shown in the figure on the left. The sequence of the sugar transport protein of metazoans including Homo sapiens was

analyzed closely as shown on the right. By combining this data with the information observed on the folding pathway obtained through magnetic tweezers, it was revealed that the structure-forming ability of membrane proteins and their capacity to transport sugars effectively both developed through an evolutionary balance. Credit: Seoul National University

Specifically, it was confirmed that the domain corresponding to half of the glucose transporter proteins located in the N-terminus contained more stable structure formations compared to the proteins from the subsequent C-terminus domain (Figure 2). Using bioinformatics, this characteristic of glucose transporter proteins was found to be conserved in all metazoan sugar transporter proteins (Figure 3). Through these observations, it can be concluded that the cell had to strike a balance in its structure by sacrificing some of its structure-forming ability in order to obtain more functionally superior membrane proteins by developing highly functional chaperones or uniquely-structured lipid molecules.

More information: Hyun-Kyu Choi et al, Evolutionary balance between foldability and functionality of a glucose transporter, *Nature Chemical Biology* (2022). [DOI: 10.1038/s41589-022-01002-w](https://doi.org/10.1038/s41589-022-01002-w)

Provided by Seoul National University

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