Map of ammonium's journey 'could prevent infection'

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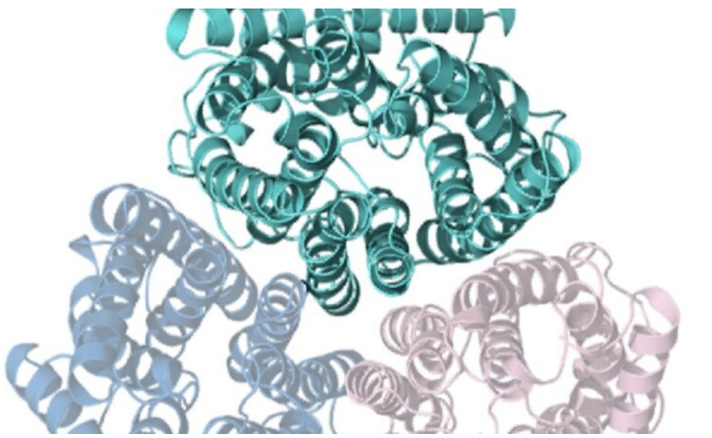

Credit: University of Strathclyde, Glasgow

The mechanism of a protein which transports ammonium across cell membranes has been discovered in research led at the University of Strathclyde, which could lay the foundations for preventing infection.

The transporting process is vital to all living things but in two distinct ways. Bacteria, fungi, and plants import ammonium as a major nutrient, using a protein called Amt, but in humans and animals, ammonium must be excreted from cells because of its toxicity; this is performed by another protein called Rh, or Rhesus antigen.

Rh is one of the proteins that is used to classify human blood groups and if the function of expelling ammonia goes wrong, it can lead to disease and death. The Rh and Amt proteins are very closely related and, despite their essential role, how they actually transport ammonium has remained elusive.

The new study, in collaboration with partners, the laboratory of Professor Ulrich Zachariae at the University of Dundee and the laboratory of the Professor Anna-Maia Marini at the Université Libre de Bruxelles, has revealed the mechanism of Amt, from the bacterium E.coli. The researchers found that Amt takes ammonium, which is naturally positively charged, from the environment and fragments into ammonia and the proton particle responsible for the positive charge. Remarkably the Amt protein from E.coli transports ammonia and the proton separately, side by side, and the then proton re-joins the ammonia on the opposite side of the membrane to reform ammonium.

The study has been published in the journal *eLife*.

Gordon Williamson, a Ph.D. student at Strathclyde, is the first lead author of the paper. He said: "Prior to our work, there was a huge controversy in the field. Based on the structure of the E. coli Amt, it shouldn't be able to transport ammonium, yet transport could be measured. Through molecular simulations, carried out by Giulia Tamburrino in the lab of our partner Ulrich Zachariae in Dundee, we discovered that the Amt protein has two chains of water molecules that run through the protein, connecting both ends. The experiments we carried out, along with further computational work, demonstrate that these water molecules act as an expressway for the proton, allowing it to bypass parts of the Amt protein that would ordinarily act as a barrier."

Professor Zachariae said "This is a good example for the high impact of computational work on present biological research. The discovery of the internal water chains by our computer simulations enabled us to connect the dots into a new transport mechanism. These findings have broad implications for understanding the transport of chemicals into and out of a cell, because failure to control this process can lead to the death of the cell."

The team is pursuing a number of follow-up projects and its next step is to understand the human ammonium transporters, the Rhesus proteins. Apart from their well-known role in blood-typing, malfunction of Rhesus proteins has also been associated with a range of diseases, from haemolytic anemia to male infertility and early-onset depressive disorders. It is hoped that the results of this work could pave the way for the development of therapies.

Co-author Dr. Arnaud Javelle, a researcher at Strathclyde Institute of Pharmacy and Biomedical Sciences, from the University of Strathclyde said: "Whilst the connection between defective Rhesus proteins and disease in humans has been known for a long time, our work will enable us to target the proteins and identify ways to treat these conditions. By improving our understanding of the normal function of ammonium transporters, we can gain insight into how specific malfunctions leads to disease."

The team is also looking to translate its research to the fungal equivalent of Amt, which is associated with pathogenicity. These pathogenic fungi can cause infection in humans and ultimately lead to death; they can also infect crop plants, severely hindering production and leading to food shortages.

Dr. Javelle said: "Our work lays the foundation for understanding how ammonium transporters contribute to fungal pathogenicity and may help prevent future infection."

More information: Gordon Williamson et al. A two-lane mechanism

for selective biological ammonium transport, *eLife* (2020). DOI: 10.7554/eLife.57183

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