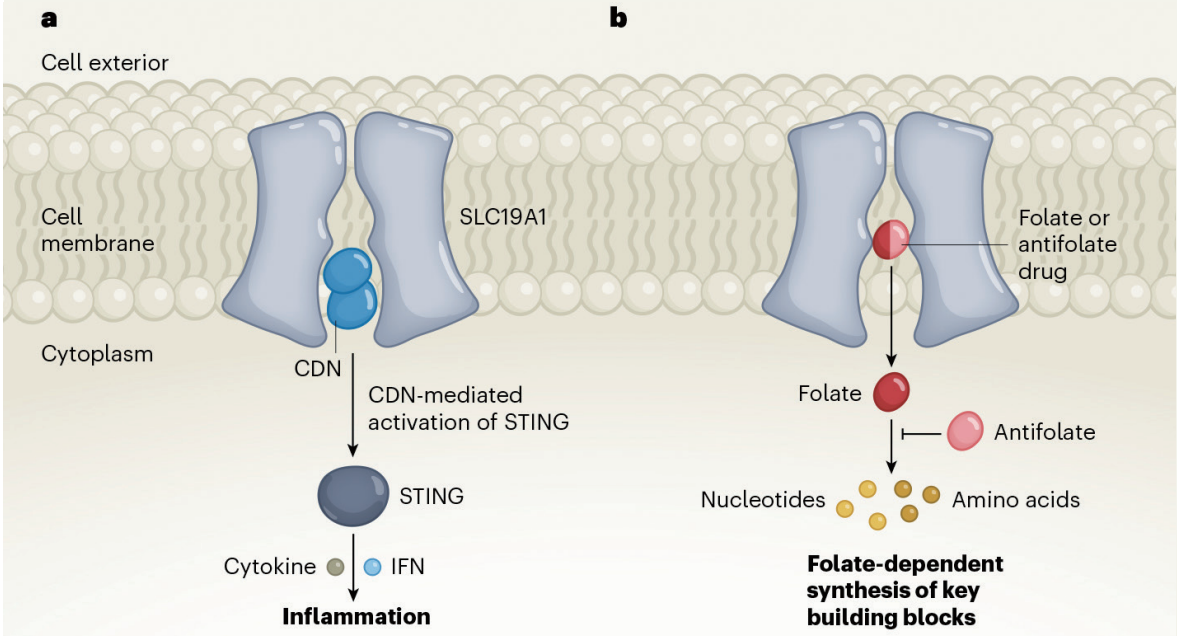
CELL BIOLOGY

Structural Insights into Folate Transporter May Offer Clues for Anticancer Drugs

By YAN Fusheng (Staff Reporter)

Researchers from the CAS Institute of Biophysics (IOB) have discovered that the transport protein SLC19A1, traditionally known for transporting B9 vitamins and antifolate drugs, is also a transporter of cyclic dinucleotides (CDNs), which are signaling molecules that stimulate immune system responses, revealing a previously unknown function that may lead to improved immunotherapy or anticancer treatments.



Structural insights into the SLC19A1 protein. (Credit: Larry H. Matherly & Zhanjun Hou/*Nature*)

A new *Nature* study published on October 20 reveals a previously unknown function of the transport protein SLC19A1, which may pave the way for the design of improved anticancer or immunotherapy treatments.

SLC19A1, also known as the reduced folate carrier, was initially studied for its role in the transportation of B9 vitamins (folates) required for certain types of nucleotide and amino-acid formation. SLC19A1 is also the primary transporter of the antifolate drugs methotrexate and pemetrexed, used in the treatment of cancer, rheumatoid arthritis, and psoriasis.

In this new study, a research team led by ZHANG Liguo and GAO Pu from the CAS Institute of Biophysics (IOB) found that SLC19A1 is also a transporter of cyclic dinucleotides (CDNs), which are signaling molecules that stimulate immune system responses.

The study used cryo-electron microscopy to determine the molecular structures of SLC19A1 with and without bound CDNs, folates, and antifolates. SLC19A1 was found to have 12 membrane-spanning segments and a positively charged substrate-binding pocket that is lined by evolutionarily conserved amino-acid residues. CDNs are crucial for activating the immune-system sensor protein STING, which drives the immune response to abnormal DNA. The recognition of SLC19A1 as a CDN transporter has opened possibilities for the design of improved immunotherapy and anticancer treatments.

However, the transport of CDNs by SLC19A1 is poor compared to the protein's ability to transport folates due to the different chemical structures of the two. Nevertheless, this discovery is a significant step forward in understanding how CDNs enter cells and how they can be utilized for therapeutic purposes.

References

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