Study suggests new mechanism for lipid transporter

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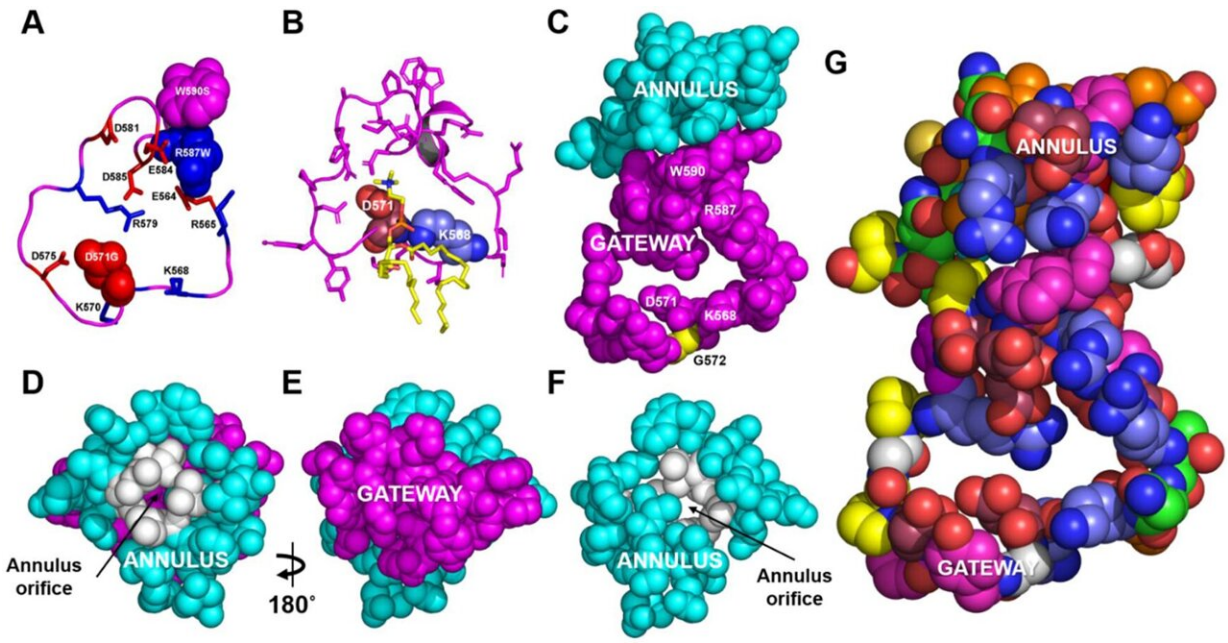

Structural details of the gateway/annulus complex. A, B The backbone of the gateway (magenta). A The basic (blue, stick) and acidic (red, stick) amino acid residues of the gateway (residues 564–592, magenta) from the ABCA1 structure determined by cryo-EM. The three amino acid residues in the gateway known to be mutated in Tangier disease (four point mutations in total) are shown in the space-filling mode. B The POPC molecule (yellow stick) forms salt-bridges to residues D571 and K568 (space-filling red and blue, respectively) in the 1.9 μsec frame during coarse-grained molecular dynamics (CGMD) modeling of unmutated ABCA1. All side chains but residues D571 and K568 are magenta stick. C The gateway (magenta)/annulus (cyan) complex. Residues of the elongated hydrophobic tunnel that lie within 10 Å of any gateway residue form the annulus domain (residues 69, 71–80, 363, and 368–379). D The annulus

(cyan) viewed from the side opposite the outward-facing transmembrane cavity. Note the small orifice (residues 73–75, 77, 78, 371, 375, colored white) in the middle of the annulus through which magenta-colored residues of the gateway on the opposite side are visible. E The base of the annulus (D) rotated 180° around the y-axis to show the gateway. The view is from the outward-facing transmembrane cavity. F Representation of the annulus with the gateway removed to display the annulus orifice. G The amino acid composition of the gateway/annulus complex. Acidic residues, rose; basic residues, blue; aromatic residues, magenta; hydrophobic residues, orange; prolines, yellow; neutral residues, green; glycines, white. Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-32437-3

A new model suggests that a protein involved in the generation of high-density lipoprotein (HDL) works differently than previously thought.

HDL is known as the "good cholesterol" because it moves fat and cholesterol away from artery walls and may help prevent or reduce atherosclerosis and coronary heart disease.

Jere Segrest, MD, Ph.D., professor of Medicine in the Division of Cardiovascular Medicine, and colleagues used computer simulation and cell culture studies to explore how the protein ABCA1 transports fatty molecules from the cell's plasma membrane to HDL. The researchers reported in the journal *Nature Communications* that ABCA1 extracts phospholipids from the outer surface of the plasma membrane, rather than the inner surface as previously thought.

"Our model of ABCA1 as an extracellular lipid transporter suggests a unique transport mechanism that differs substantially from mechanisms described for other members of this transporter family," Segrest said. "This surprising finding highlights the remarkable diversity in substrate transport within the ABCA transporter superfamily.

"These insights into the mechanism of ABCA1 transport are important because they point towards potential pathways for promoting ABCA1-dependent phospholipid and cholesterol efflux from cholesteryl ester-laden macrophages, which play key roles in all stages of atherosclerotic lesion development," Segrest added.

Hyun Song, Ph.D., research assistant professor of Medicine, used coarse-grained and steered molecular dynamic simulations to show that a "gateway" domain of ABCA1 removes phospholipids from the outer side of the membrane and passes them through a ring-shaped "annulus" domain into a fatty-lined (hydrophobic) tunnel.

Collaborators Chongren Tang, Ph.D., and Jay Heinecke, MD, at the University of Washington, Seattle, engineered mutations in the gateway and annulus domains of the ABCA1 transporter and found that the mutations strongly inhibited lipid export by ABCA1 without affecting transporter cell-surface expression.

More information: Jere P. Segrest et al, ABCA1 is an extracellular phospholipid translocase, *Nature Communications* (2022). DOI: 10.1038/s41467-022-32437-3

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