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COMMENTARY

Turning a Reference Inside-Out: Commentary on an Article by Stevens and Arkin Entitled: "Are Membrane Proteins 'Inside-Out' Proteins?" (Proteins 1999;36:135–143)

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Although we would generally be flattered to be cited as originators of a "central paradigm of structural biology," this was not the case when Stevens and Arkin[1] recently attributed the idea that membrane proteins are "inside-out" proteins to our very article[2] that discredited this model 10 years ago. Our commentary is prompted by these authors' report[1] "Are Membrane Proteins 'Inside-Out' Proteins," which starts: "One of the central paradigms of structural biology is that membrane proteins are 'inside-out' proteins, in that they have a core of polar residues surrounded by apolar residues." Three references are provided for this claim—two from our groups[2,3] and the third[4] that actually introduced the inside-out organization concept for the proton-pumping protein bacteriorhodopsin. After an analysis of the distribution of polar and apolar residues in the transmembrane region of integral membrane proteins, Stevens and Arkin conclude that "based on the data set used, membrane proteins as 'inside-out' proteins is an unfounded notion, suggesting that packing of α-helices in membranes is better understood by maximization of van der Waal's forces, rather than by a general segregation of hydrophobicities driven by lipid exclusion." We are gratified that these observations reinforce our conclusions from 1989[2] that both buried and surface exposed residues in the transmembrane regions of membrane proteins are apolar. The main point of our article is stated directly in the abstract: "The hydrophobicities of interior residues of both membrane and water-soluble proteins are comparable, whereas the bilayer exposed residues of membrane proteins are more hydrophobic than the interior residues, and the aqueous-exposed residues of water-soluble proteins are more hydrophilic than the interior residues." It is difficult to understand how this statement could be interpreted by Stevens and Arkin as a claim by us that membrane proteins have a polar core; their remark on p. 139 that "Rees and co-workers . . .; conclude that in . . . [the photosynthetic reaction center] a polar core does exist" could not more completely turn our conclusions "inside-out." Table 1 of our article[2] clearly and quantitatively demonstrates that residues in the interior of the reaction center are as apolar as residues in the interior of water-soluble proteins.

As a "paradigm," the inside-out model for membrane protein structure is no longer generally accepted. For example, Lemmon and Engelman[5] comment that "The distinction to be made between soluble and membrane proteins is that the interiors are similar, but the lipid-facing portions of the latter are, as one might expect, rather more apolar than the solvent exposed regions of the former," and White and Wimley[6] in their recent review conclude that "The early hypothesis that membrane proteins might be 'inside-out proteins' stabilized mostly by polar interactions does not appear to be correct." Concerning differences in hydrophobicity between surface exposed and buried residues in the transmembrane region of membrane proteins, we note that Wallin et al.[7] arrived at conclusions similar to ours, using a database containing ~75% of the transmembrane helices examined by Stevens and Arkin. Finally, the comment by Stevens and Arkin that van der Waals interactions are important for membrane protein structure parallels our concluding statement:[2] "An implication of this view is that van der Waals forces among the many atoms in the close-packed interiors of both membrane and water-soluble proteins are crucial for protein stability."

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