Qeios

Peer Review

Review of: "Decoding the Promiscuous Activity of Bile Salt Hydrolase"

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This commentary provides an intellectually stimulating and mechanistically focused interpretation of the recent findings by Rimal et al. on bile salt hydrolase (BSH)-mediated formation of bacterial bile acid amidates (BBAAs). The authors propose that the observed N-acyltransferase activity represents **condition promiscuity**, aligning it with well-established principles of micellar enzymology. The conceptual framing is elegant and grounded in enzymology literature, particularly the distinction between substrate, catalytic, and condition promiscuity. The argument that bile salts act dually as substrates and micelle-forming surfactants is mechanistically plausible and represents a creative extension of micellar catalysis principles into a physiological context. The proposed experimental tests—below-CMC reactions and alternative surfactants—are concrete and testable, which strengthens the commentary.

Alternative Mechanistic Explanations

The commentary frames the activity exclusively as condition promiscuity. However:

It should briefly acknowledge alternative possibilities, such as genuine catalytic promiscuity driven by altered substrate positioning.

Structural or kinetic data from Rimal et al. could be discussed more explicitly to support the condition-promiscuity interpretation.

Thermodynamic Considerations

Amidation in aqueous environments is generally disfavored thermodynamically. A short discussion of how micellar compartmentalization may shift equilibrium (e.g., water exclusion effects) would add depth.

Structural Aspects of BSH

Since BSH enzymes are N-terminal nucleophile hydrolases, the commentary could briefly mention how the catalytic cysteine mechanism accommodates reversal under altered water activity.

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Scope and Limitations

The claim of “first in vivo demonstration” should be tempered unless supported by literature excluding similar phenomena.

Minor Points

A brief schematic illustration (even conceptual) of micelle-assisted amidation would enhance clarity.

The language could slightly distinguish between “reverse hydrolysis” and “synthetic transfer,” as mechanistically they may differ in kinetic pathways.

Declarations

Potential competing interests: No potential competing interests to declare.