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The distribution and mechanism of iodotyrosine deiodinase defied expectations

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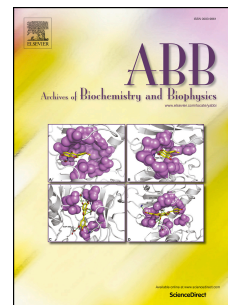
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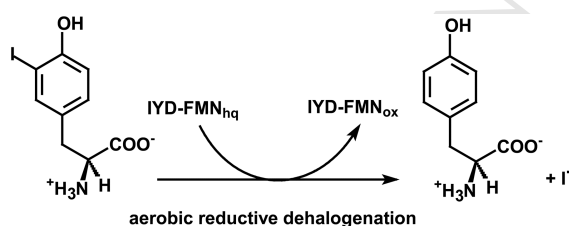
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Graphic abstract



Abstract:

Iodotyrosine deiodinase (IYD) is unusual for its reliance on flavin and ability to promote reductive dehalogenation under aerobic conditions. As implied by the name, this enzyme was first discovered to catalyze iodide elimination from iodotyrosine for recycling iodide during synthesis of tetra- and triiodothyronine collectively known as thyroid hormone. However, IYD likely supports many more functions and has been shown to debrominate and dechlorinate bromo- and chlorotyrosines. A specificity for halotyrosines versus halophenols is well preserved from humans to bacteria. In all examples to date, the substrate zwitterion establishes polar contacts with both the protein and the isoalloxazine ring of flavin. Mechanistic data suggest dehalogenation is catalyzed by sequential one electron transfer steps from reduced flavin to substrate despite the initial expectations for a single two electron transfer mechanism. A purported flavin semiquinone intermediate is stabilized by hydrogen bonding between its N5 position and the side chain of a Thr. Mutation of this residue to Ala suppresses dehalogenation and enhances a nitroreductase activity that is reminiscent of other enzymes within the same structural superfamily.

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