Accepted Manuscript

The distribution and mechanism of iodotyrosine deiodinase defied expectations

Zuodong Sun, Qi Su, Steven E. Rokita

PII: S0003-9861(17)30379-X

DOI: 10.1016/j.abb.2017.07.019

Reference: YABBI 7529

To appear in: *Archives of Biochemistry and Biophysics*

Received Date: 12 June 2017

Revised Date: 24 July 2017

Accepted Date: 30 July 2017

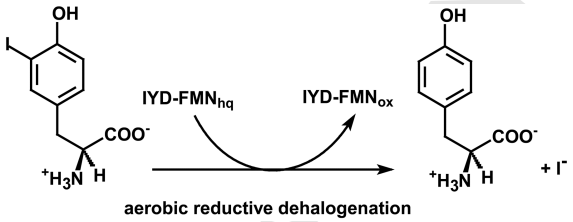
Please cite this article as: Z. Sun, Q. Su, S.E. Rokita, The distribution and mechanism of iodotyrosine deiodinase defied expectations, *Archives of Biochemistry and Biophysics* (2017), doi: 10.1016/j.abb.2017.07.019.

title: The Distribution and Mechanism of Iodotyrosine Deiodinase Defied Expectations

authors	Zuodong Sun, Qi Su and Steven E. Rokita
affiliations	Department of Chemistry, Johns Hopkins University 3400 N. Charles St., Baltimore, MD 21218 USA
corresponding author	Steven E. Rokita (rokita@jhu.edu)

keywords	Flavin, dehalogenase, thyroid, iodide salvage, reductive dehalogenation

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.