Chemical biologists find new halogenation enzyme

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Molecules containing carbon-halogen bonds are produced naturally across all kingdoms of life and constitute a large family of natural products with a broad range of biological activities. The presence of halogen substituents in many bioactive compounds has a profound influence on their molecular properties.

One of the Holy Grails in chemical science has been to find the late-stage, site-specific incorporation of a halogen atom into a complex natural product by replacing an sp^3 C-H bond (one of the most inert chemical bonds known in an organic compound) with a C-X bond (X=halogen). Until work was undertaken in the laboratory of Xinyu Liu at the University of Pittsburgh, there was no reliable synthetic or biological method known to be able to achieve this type of transformation.

In an article published online on Sept. 14 in *Nature Chemical Biology*, the group, led by Liu, an assistant professor of chemistry within Pitt's Kenneth P. Dietrich School of Arts and Sciences, has discovered the first enzyme that can accomplish this feat.

Liu and postdoctoral fellow Matthew Hillwig studied bacteria and demonstrated that the WelO5 protein is the first enzyme identified to have the capacity to mediate the regio- and stereospecific replacement of an aliphatic C-H bond to C-Cl bond on a freestanding small molecule. Specifically, they determined this by studying the biogenesis of hapalindole-type alkaloid welwitindolinones in stigonematalean

cyanobacteria.

Their work also provides conclusive evidence on a longstanding question regarding the enzymatic origin of chlorine substitution in the biogenesis of hapalindole-type alkaloids in accordance with a proposal that was recently formulated by the Liu group.

It is expected that this discovery will present unprecedented opportunities to evolve new catalysts for selective late-stage halogenations on unactivated carbons in complex molecular scaffolds.

This development could find broad applications in pharmaceutical and agricultural industries, enabling medicinal chemists to tailor synthetic molecules with halogen substituents in order to improve their pharmacological profiles.

More information: *Nature Chemical Biology*, www.nature.com/nchembio/journa … l/nchembio.1625.html

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