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Acetohydroxyacid synthase regulation, structure and inhibition by commercial herbicides

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Acetohydroxyacid synthase (E.C. 2.2.1.6) is the first enzyme in the branched chain of amino acid biosynthesis pathway. It is the target of five classes of commercial herbicides (i.e. sulfonylureas, imidazolinones, triazolopyrimidines, pyrimidinyl-benzoates, sulfonylamino-carbonyl-triazolinones), which are popular amongst famers worldwide due to their extremely high potency, low toxicity to animals and high selectivity for weeds over crops. Although AHAS is of high importance, some aspects of the enzyme structure, function and inhibition have remained unresolved. Here we show that FAD reduction is required for AHAS activity and that soluble quinone derivatives (e.g. ubiquinones) regulate this activity by oxidizing FAD and by a slow process of FAD re-reduction. A new high-resolution structure of *Saccharomyces cerevisiae* AHAS (2 Å) reveals FAD is trapped in two different conformations indicative of two oxidation states occurring at the same time. Moreover, this structure shows the position of two oxygen molecules in the active site and an oxygen access channel. In addition, we have determined the crystal structures of un-inhibited *Arabidopsis thaliana* AHAS and in complex with herbicides of the pyrimidinyl-benzoate and sulfonylamino-carbonyl-triazolinone families. These structures show that the herbicide binding site in plant AHAS adopts a folded state even in the absence of herbicide. This is unexpected because the equivalent regions in yeast AHAS are disordered or have a different folding. These structures and mass spectrometry show that the herbicides trigger an alteration of the enzyme cofactor thiamine diphosphate. Kinetic studies show that all five families of herbicides elicit accumulative inhibition of the enzyme, which is linked to thiamin diphosphate degradation. These features contribute to the extraordinary potency of these herbicides when in action.

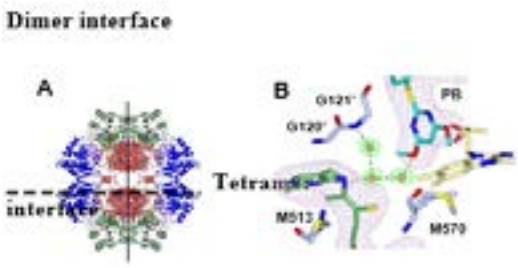

Figure1: *(A) Crystal structure of A. thaliana AHAS3. (B) Herbicide binding site of A. thaliana AHAS in complex with pyrithiobac, showing the degradation of the thiamin diphosphate cofactor4.*

Biography

Mario Daniel Garcia is in his third year of PhD studies at The University of Queensland, Australia. He obtained his Bachelor's degree (Hons.) in Biotechnology at Universidad de las Fuerzas Armadas, Ecuador, in 2010. His research work has focused on understanding the structure, function and inhibition of plant and yeast acetohydroxy acid synthase, with a special interest in describing the role of commercial herbicides that target AHAS have in the degradation/modification of thiamin diphosphate.

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