A cascade of redox reactions in the biosynthesis of the protein phosphatase-2A inhibitor rubratoxin A

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With the support by the National Natural Science Foundation of China, a collaborative study by the research groups led by Prof. Hu Youcai (**胡友财**), Prof. Yu Shishan (**庾石山**) and Prof. Tang Yi (**唐奕**) from the State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College elucidates the biosynthetic mechanism of protein phosphatase-2A inhibitor rubratoxin A, which was published in *Angewandte Chemie International Edition* (2017, 56: 4782—4786).

Fungi are a very important source of bioactive natural products and clinical medicine, in which nonadride fungal natural products have attracted much attention from chemists and biologists due to its complicated structure and significant biological activity. Structurally, rubratoxins belong to the family of nonadrides with a cyclononane ring and two fused maleic anhydrides to form the 5/9/5 core ring system. The unique structure of rubratoxin A makes it a highly specific and potent inhibitor of protein phosphatase 2A (PP2A), and thus a potential lead compound for the development of anticancer drugs. Understanding the biosynthesis of rubratoxin A could therefore provide significant new insight into how nature builds structural complexity and unusual biosynthetic features starting from relatively simple precursors.

In this study, researchers identified the biosynthetic pathway of rubratoxin A and completely mapped the enzymatic sequence of redox reactions starting from a simple nonadride. Six redox enzymes are involved, including four α-ketoglutarate and iron(II) dependent dioxygenases that hydroxylate four sp^3 carbons, one flavin-dependent dehydrogenase that is involved in formation of the unsaturated lactone, and a ferric-reductase like enzyme RbtH which regioselectively reduces one of the maleic anhydride moieties in rubratoxin B into the γ-hydroxybutenolide that is critical for PP2A inhibition. RbtH is proposed to perform sequential single-electron reductions of the maleic anhydride using electrons derived from NADH and transferred through a ferredoxin and ferredoxin reductase pair.

The results show that how the fungus "drug factory" utilized the complex oxidase system to convert a simple inactive maleic anhydride dimer to a structurally complex mycotoxin and further to a promising antitumor agent by the reductase system, demonstrating the amazing of Nature.

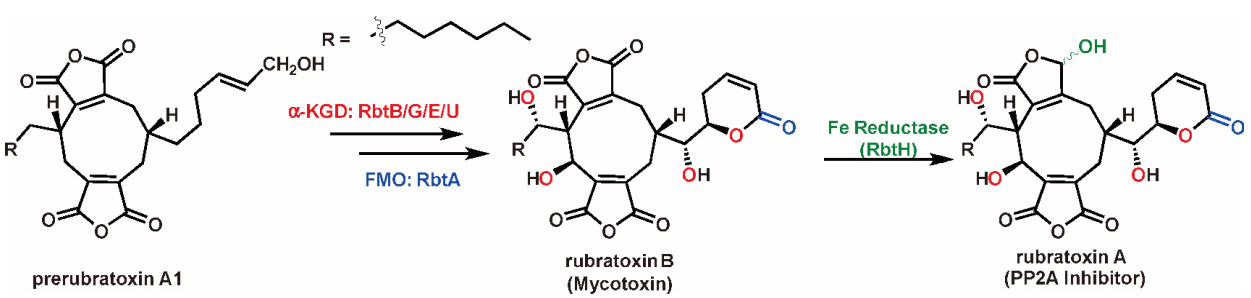

Figure The biosynthetic mechanism of protein phosphatase-2 inhibitor rubratoxin A.