Discovery of the Fundamental Mechanism of Action of Resveratrol

Resveratrol is reported to extend lifespan and provide cardio-neuro-protective, anti-diabetic, and anti-cancer effects by initiating a protective stress response. Resveratrol is produced in grapes, cacao beans (dark chocolates), peanuts (peanut butter), Japanese knotweed, blueberries and some other plants, in response to environmental stress conditions including infection, drought and ultraviolet radiation. Schimmel's laboratory is known for its work on an ancient family of enzymes, the aminoacyl tRNA synthetases. These enzymes establish the genetic code by linking nucleotide codons to amino-acid building blocks that make proteins. But emerging research from Schimmel's group and others over the past decade demonstrated that tRNA synthetases have progressively acquired an extensive set of other functions in higher organisms. Their previous work suggested that the amino acid binding site of tRNA synthetases might be exploited by natural amino acid analogues to modulate the non-translational functions of tRNA synthetases (1). Because resveratrol has a structure similar to the amino acid tyrosine, they hypothesized that it might therefore bind to TyrRS to stimulate its non-translational functions (Human TyrRS is a homodimer of a 528 amino-acid polypeptide that harbors an appended eukaryote-specific carboxy (C)-terminal EMAP-II domain).

Using x-ray diffraction data collected from Beam Line 11-1 at SSRL, Sajish and Schimmel solved the crystal structure of resveratrol and tyrosine bound to the active site of TyrRS at 2.1 Å resolution (Figure). The findings address some of the mystery and controversy about the mechanism of action of resveratrol. The binding of resveratrol to TyrRS blocked its role in protein synthesis in the cytoplasm and triggered its non-translational function in the cell nucleus, where it activates another protein, PARP-1, a major stress response and DNA-repair factor believed to have an influence on longevity. PARP1 is the major determinant of the nicotinamide dinucleotide ($NAD^{+)}$ content of cells. (NAD^{+} content is believed linked to aging). The interaction and functional activation of PARP1 in mice injected with resveratrol was shown, where TyrRS's stimulation of PARP1 led to the NAD^{+}-dependent activation of protective genes, including the tumor-suppressor gene *p53* and the longevity-associated genes *FOXO3A* and *SIRT6*.

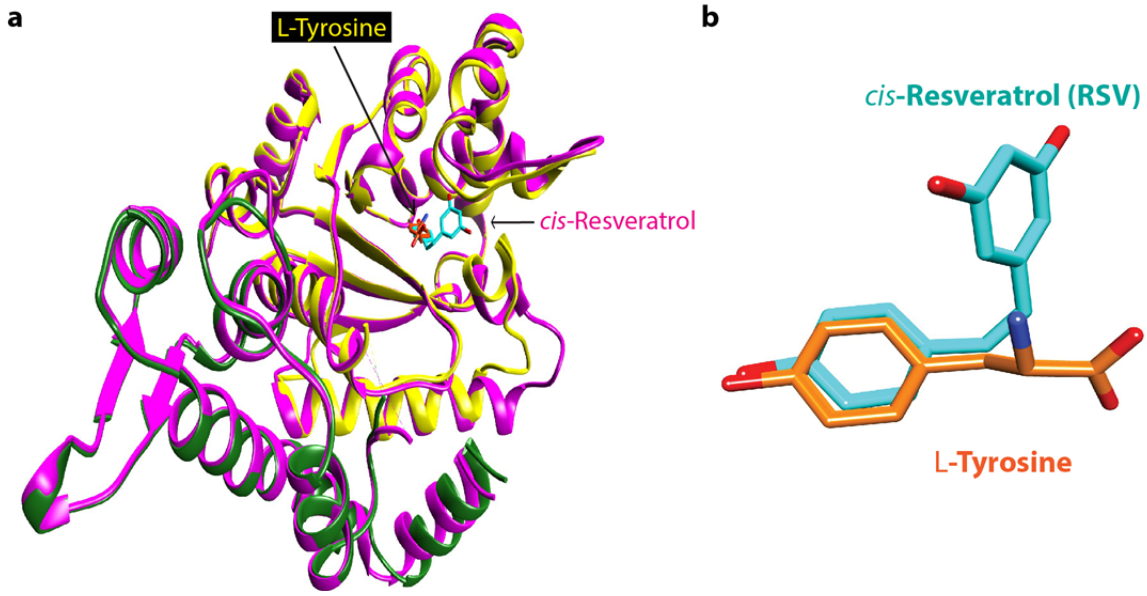

Figure: **a,** Structural superposition of the co-crystal x-ray structures (2.1 Å) of TyrRS bound to *cis*-resveratrol and to L-tyrosine (yellow, tyrosine-bound structure; magenta, resveratrol-bound structure). Resveratrol induces an overall conformational change with a distinct local conformational change relative to bound tyrosine near the active site. **b**, Superposition of *cis*-resveratrol and to L-tyrosine bound at the active site of TyrRS depicting the amino acid mimicry by resveratrol.

The newly discovered signaling pathways –a layer of biology that had been largely overlooked – further demonstrated how resveratrol might be beneficial at the cellular level. Strikingly, relatively small quantities of resveratrol were enough to trigger protective effects in an animal. These amounts were 10- to as much as 100 times smaller than previously thought effective. Thus, the higher doses used in prior work had effects that were layered over this more sensitive pathway.

Primary Citation

M. Sajish and P. Schimmel, "A Human tRNA Synthetase is a Potent PARP1-activating Effector Target for Resveratrol", *Nature* **8**, 547 (2015), DOI: 10.1038/nature14028.

References

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Contacts

Mathew Sajish, The Scripps Research Institute

Paul Schimmel, The Scripps Research Institute

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