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Confluence of structural and chemical biology: plant polyketide synthases as biocatalysts for a bio-based future

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Type III plant polyketide synthases (PKSs) biosynthesize a dazzling array of polyphenolic products that serve important roles in both plant and human health. Recent advances in structural characterization of these enzymes and new tools from the field of chemical biology have facilitated exquisite probing of plant PKS iterative catalysis. These tools have also been used to exploit type III PKSs as biocatalysts to generate new chemicals. Going forward, chemical, structural and biochemical analyses will provide an atomic resolution understanding of plant PKSs and will serve as a springboard for bioengineering and scalable production of valuable molecules *in vitro*, by fermentation and *in planta*.

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Introduction

Type III polyketide synthases (PKSs) including chalcone synthases (CHSs) and the related stilbene synthases (STSs) are a large family of condensing enzymes first discovered in plants [1]. These once underappreciated PKSs are now known to generate an overwhelming array of small molecules important to plant survival and fitness and to human health and nutrition (Figure 1). In a reaction sequence divergently related to fatty acid anabolism, type III PKSs biosynthesize a polyketide chain through decarboxylative condensation of malonyl-Coenzyme A (CoA) derived two-carbon units (Figure 2a). The resultant chemically reactive chain undergoes tautomerization into keto and enol (enolate) substructures. Specific tautomers, favored by the PKS catalytic environment, then direct cyclization and offloading of polyphenolic chemicals (Figure 2b).

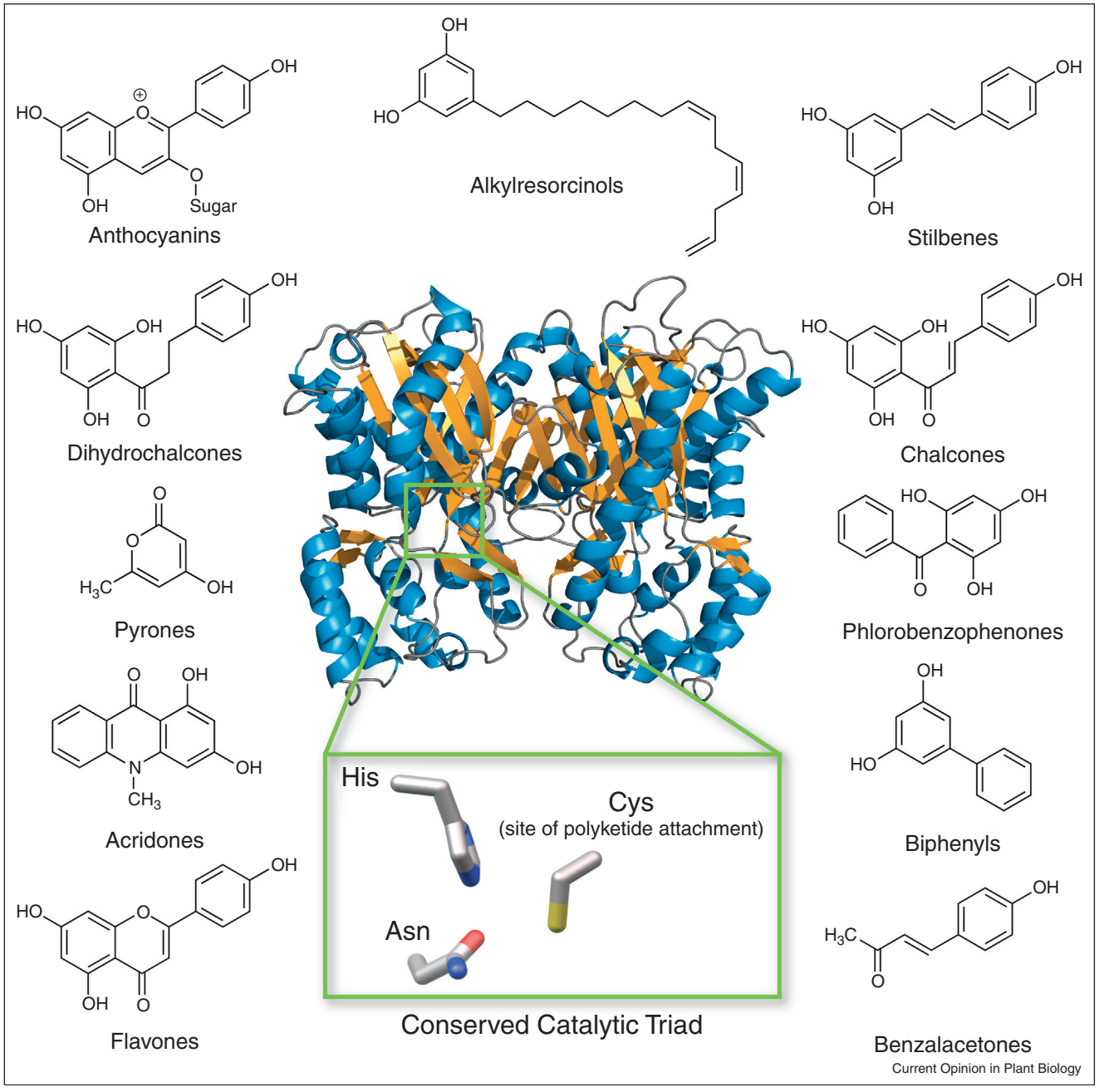
Phenolic compounds were likely early physiological adaptations, accelerating the movement of plants from aquatic to terrestrial environments [2,3]. Contemporarily, polyketides serve a wide range of adaptive roles in plants, including UV protection, flower color, pollen development, root nodulation, plant architecture, and chemical defense; plant polyketides also contribute to the astringent and bitter flavors of many foods and beverages [4–7]. The growing appreciation for the diversity of *in vivo* functions of type III PKSs is mirrored by the varied medicinal properties of their products. Stilbenes found in the skin of grapes and other fruits slow aging in model organisms [8,9]. The antioxidant capacity of flavonoids correlates with cancer prevention, and new research is exploring the potential of flavonoids to ameliorate complications from diabetes and nervous system disorders [10,11]. Curcuminoids found in turmeric are effective inhibitors of cancer and inflammation [12].

The critical role of type III PKSs to plant metabolism and adaptation, their contribution to healthier foods and medicines, and their expanding role as biocatalysts in renewable chemical production, is attracting researchers from diverse areas of science and engineering. This article highlights the role of small molecule tools specifically designed to further our understanding of type III PKS structure and function and to expand the central role of type III PKSs in burgeoning biorenewables industries.

Architectural simplicity tied to catalytic complexity

Type III PKSs are homodimeric proteins that use CoA tethered substrates to carry out thioester exchange reactions, polyketide chain-elongation, and select cyclization paths in a single active site. Their architectural simplicity combined with their catalytic potential make type III PKSs extremely attractive targets for the engineering of efficient and manipulatable biocatalysts. Each dimer encapsulates a large internal cavity which lies at the end of a CoA binding tunnel [13]. Type III PKSs initiate their reactions by binding an acyl-CoA and loading the acyl group onto an active site cysteine (Figure 1). The reaction continues with iterative rounds of decarboxylative condensation of two-carbon units derived from malonyl-CoA (Figure 2a).

Figure 1



Molecular diversity in type III PKS catalysis. A homodimer of a type III PKS illustrated as a ribbon diagram with helices colored blue, β-sheets colored orange and loops colored gray. The two-fold dimerization axis is vertical to the page. Surrounding the protein structure are examples of phytochemicals derived from type III PKS metabolic pathways. The conserved catalytic triad — His-Cys-Asn is shown in close-up below the ribbon diagram and highlighted by a green box.

How the PKS active site tames and redirects the high intrinsic reactivity of growing poly-beta-ketides remains unclear [1]. What is clear is that the reaction terminates through regiospecific cyclization (Figure 2b). Notably, natural and directed evolution have exploited one or more of these three phases of the reaction cycle to generate product diversity [14,15••]. Structural enzymology is clarifying how steric, dynamic, and electronic factors focus the multiple points of chemical reactivity in elongated polyketides to modulate chain length selectivity and discriminatory bond formation during reaction termination [16–19].