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Spotlight

Ancient enzyme diversification underpins octocoral chemical diversity

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Burkhardt *et al*. reveal that diterpene synthases diversified early in octocoral evolution, resulting in functionally conserved clades across lineages. Their findings highlight octocorals as an exciting system to study the evolutionary origins and dynamics of terpene synthase enzymes in animals.

Organisms across the tree of life produce a vast diversity of specialized metabolites that vary in ecological function, mediating many critical processes such as defense and communication. This natural chemical diversity is also important to humans, providing a rich source of economically and pharmaceutically valuable compounds. However, we are only beginning to understand how biosynthetic pathways evolve and diversify to generate novel compounds. Terpenes are the largest and most structurally varied class of natural products. Their five-carbon precursors isopentenyl diphosphate and dimethylallyl diphosphate are derived from a conserved essential metabolic pathway that produces, for example, sterols. From these building blocks, isoprenyl diphosphate synthases (IDSs) generate substrates of varying lengths that terpene synthases (TPSs) convert into a vast array of scaffolds [1].

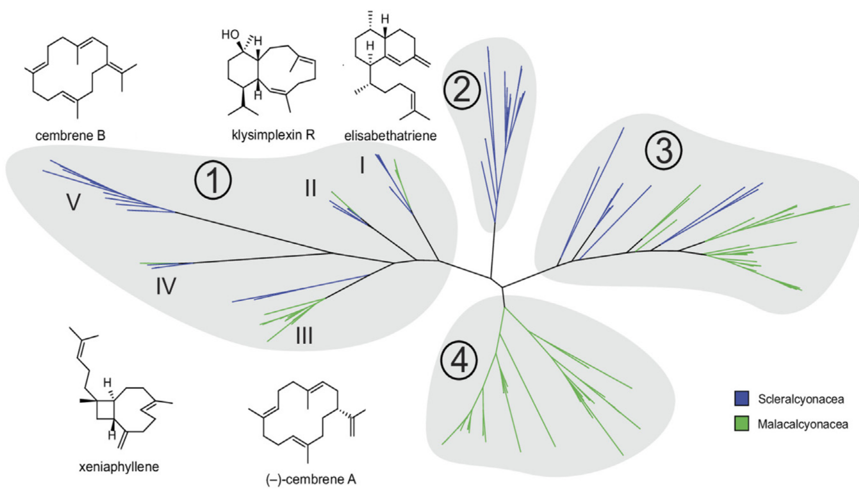
For many years, canonical TPS genes were thought to be absent in animals. Although animals metabolize the necessary precursors for terpene production, they were believed to rely on sequestration from plants or microbial symbionts [2]. This view changed when insects were shown to synthesize terpenes *de novo* through the co-option of primary metabolic IDS genes [3–5]. Even more unexpectedly, canonical TPS enzymes, long considered to be restricted to plants, fungi, and microbes, have now been discovered in several animal lineages, such as arthropods [6] and corals [7,8]. These findings suggest that terpene biosynthesis is far more ancient and taxonomically widespread than previously recognized.

Despite the growing list of lineages with canonical TPSs, the timing and mechanisms by which these enzymes have diversified remain unclear. A recent study in *Proceedings of the National Academy of Sciences* [9] addresses this gap by tracing the early evolutionary dynamics of TPSs in octocorals (a group representing approximately half of all corals, including soft corals, sea pens, and blue corals [7]). In marine environments, they are a primary source of chemical diversity, producing more than a tenth of known marine natural products. In terms of terpenes, they primarily produce sesquiterpenes (15-carbon terpenes) and diterpenes (20-carbon terpenes), which are thought to provide octocorals with chemical defense. Not only are they of interest from an evolutionary perspective (as terpene-producing animals), but also many described octocoral compounds show pharmaceutical potential. Most octocoral research has focused on species found in shallower, warmer waters, but less attention has been paid to deep-sea corals, primarily due to difficulties in access. In this study, the authors investigate the genetic and chemical diversity of deep-sea corals. They discover distinct functional TPS clades and show that key diterpene synthase activities emerged early in octocoral evolution, revealing how terpene biosynthesis has evolved and diversified in this group.

Burkhardt *et al*. combine comparative genomics, biochemical assays, and phylogenetics to reconstruct the origins and diversification of TPSs in octocorals. By profiling terpenes across nine distantly related deep-sea octocorals, they uncover extensive variation in sesquiterpene production. By contrast, a more restricted set of diterpenes was found, many corresponding to compounds that have been previously identified in corals. Expanding their dataset with published diterpene structures, they classify octocoral diterpenes into five major scaffold categories based on their likely biosynthetic precursors. The widespread distribution of four of these scaffold categories across octocoral lineages suggests that these underlying biosynthetic innovations are ancient.

The authors integrate high-quality genome assemblies with publicly available TPS sequences to reveal four major TPS clades (Figure 1). Clade 1 is particularly notable. It contains five subclades, four of which include sequences from both major octocoral lineages, implying that diversification occurred prior to the split of these lineages. A striking insight from functional assays is that each subclade produces a distinct diterpene scaffold (Figure 1). Remarkably, reconstructed ancestral sequences at the base of each subclade also produce the expected scaffolds. The other clades (2–4) are primarily associated with sesquiterpene production and exhibit little functional conservation. Such strong correspondence between subclade and enzyme activity in clade 1 suggests that functional specialization of diterpene synthases arose early and was maintained throughout octocoral diversification.

Interestingly, this pattern is similar to the evolution of terpene synthesis in plants. The ancestral plant TPS function (producing *ent*-kaurene, a diterpene scaffold) is conserved, followed by



Trends in Biochemical Sciences

Figure 1. Four TPS clades, with clade 1 showing ancient diversification into five subclades. Each clade 1 subclade produces one of the five conserved diterpene scaffolds that underlie octocoral terpene diversity. Figure adapted from [9].

extensive lineage-specific diversification to produce the remarkable diversity of plant terpenes [10]. Such parallels suggest that perhaps there are general evolutionary principles that govern how biosynthetic pathways evolve.

These findings reveal the deep evolutionary origins of terpene biosynthesis in octocorals, potentially even cnidarians. Burkhardt *et al*. propose two hypotheses for the origins of this pathway: (i) the last common ancestor of octocorals acquired a TPS gene via horizontal gene transfer from a microbial source, followed by rapid duplication before octocoral diversification; or (ii) the last common cnidarian ancestor already had terpene biosynthetic capacity that was then lost in other cnidarian lineages. Distinguishing between these scenarios will require broader sampling of cnidarians and other animal lineages.

By reconstructing when and how diterpene synthases diversified in octocorals, this study provides a powerful framework for understanding how metabolic novelty arises, persists, and radiates to produce an array of compounds. Similar functionally conserved TPS clades have been described in plants. However, none so far have been found in other terpene-producing animals, such as insects that have co-opted IDS enzymes for TPS function. With the recent discovery that some arthropods also have canonical TPS genes [6], it will be interesting to see whether the evolutionary dynamics in these groups are more similar to canonical TPS evolution in octocorals or noncanonical TPS evolution in other insects. New genomic tools have opened the door to studying how terpene synthesis has evolved in a wide range of lineages. This will allow us to explore the evolutionary principles governing how biosynthetic pathways evolve and diversify.

Declaration of interests

The author declares no competing interests.

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