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Commentary

Irregular Terpene Synthase Substrates: A New Facet of the Bacterial Terpene Metabolism

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ABSTRACT

Aberrant from the 'isoprene rule' the terpene synthases of the non-canonical terpene biosynthesis pathway detected in bacteria use methylated and cyclized substrates. The altered substrate spectrum of terpene synthases additionally enlarges the already huge terpene diversity and adds another facet to the fascinating terpene metabolism.

Keywords: Bacteria; Isoprene rule; Terpene; Metabolism

DESCRIPTION

The isoprene rule was coined by Otto Wallach (1887) and Leopold Ruzicka (1953). This hypothesis was the basis to unravel the structures of high molecular weight compounds such as cholesterol and steroid hormones. It proposed that C5-building blocks such as isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DAMPP) are the principle for the wealth of terpenoids which are subsequently polymerized to form the canonical prenyldiphosphates such as geranyl pyrophosphate (GPP), farnesyl pyrophosphate (FPP) etc. The successive acting terpene synthases are predestined to enlarge the terpenoid variety because they can act as single product as well as multiproduct enzymes. Furthermore, product variety is enhanced due to the action of decorating enzymes such as cytochrome P450 oxygenases, dehydrogenases, methyltransferases, acyltransferases and glucosyltransferases.

It was always a mystery or at least unusual that during evolution the number of known substrates of terpene synthases remained small. Apparently, the active pocket was highly specific for acyclic substrates of multiples of C5 such as IPP, DMAPP, GPP, NPP (nerylpyrophosphat), E- and Z-FPP etc. Consequently, compounds of 5-fold carbon atoms are expected unless post-biosynthesis modifications occur. Apparently, the isoprene rule was for more than 120 years so convincing that substrate variability of terpene synthases was not expected or searched for. Only 2008, 2-methyl-GPP was demonstrated to be a substrate [1,2] to reveal the C11 compounds 2-methylisoborneol and 2-methylbornane, respectively. This variation is particularly present in Actinobacteria (e.g. Streptomyces species). During elucidation of the biosynthesis of the unique and extraordinary compound sodorifen (C16H26) from Serratia plymuthica 4R × 13 it came as a surprise that methylated and cyclized FPP (C16 compound; named presodorifen) was the substrate for the following terpene synthase (SODS, sodorifen synthase) [3]. Indeed, we could show that a specific methyltransferase uses solely FPP (not GPP or GGPP) as substrate to methylate at position 10 which subsequently allows an unusual cyclization reaction. The FPPMT is of specific interest since in addition to the methylation a cyclization reaction builds a pentyl ring by using tyr 39 and his 191 as catalytic dyade. This new class of methyltransferases which uses prenyldiphosphates as substrates are collectively named isopentenyl diphosphate methyltransferases (IDMTs) [4] (Figure 1).

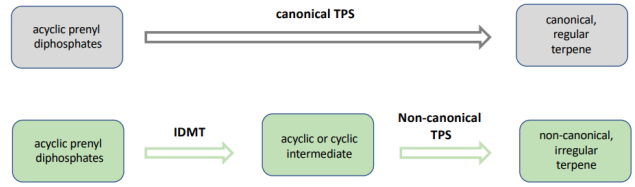

Figure 1: Scheme presenting the classical terpene biosynthesis (upper panel) and the new non-canonical bacterial terpene biosynthesis (lower panel). TPS: Terpene synthase, IDMT: Isopentenyl diphosphate methyltransferase.

Beside the fascinating reaction of the FPPMT the subsequent acting terpene synthase is also unusual as this enzyme solely accepts the cyclic substrate presodorifen. Apparently, the active pocket of the SODS adapted to a cyclic compound. So far, only the Kaurene Synthase (KS) of the gibberellin biosynthesis is known to accept

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a cyclic substrate (copalyl pyrophosphate, CPP). However, both enzymes, the SODS and KS, use very different cyclic substrates, SODS exploites a 5-ring while KS accepts a 6-ring bicyclic intermediate. Furthermore, the SODS is thought to perform a complex reaction mechanism by opening the 5-ring of presodorifen to rearrange it to a different 5-ring and an additional 6-ring, while the KS uses the methylation of CPP to complete a 6-ring. Since the majority of terpene synthases accept acyclic substrates it presently can only be speculated how the active pocket of SODS evolved, although this feature might not come as a surprise since terpene synthases are the world champions in cyclization reactions!

The genetic analysis of IDMTs showed that they cluster together with terpene synthase genes, while decorating methyltransferases were to date not found in this Biosynthetic Gene Clusters (BGC). With this knowledge it will be possible to find new irregular terpenes independent of cultivation conditions and without understanding the regulation of gene expression. Furthermore, the terpene metabolism of the bacteria can be reconsidered, regarding the usage of a special pool of non-canonical substrates. These results furthermore also indicate why the access to the bacterial terpenome might have been difficult in the past, but it also shows nicely the bag of tricks present in the world of bacteria! Considering the high number of bacteria expected to exist on earth (1012 species) and the so far rather small number of known bacterial terpene synthases new and interesting BGCs might be detected. In the future, it will be interesting to address the following questions: which advantage have bacteria producing this kind of irregular terpenes? Is this new biosynthetic pathway younger or older than the canonical pathway? Is the non-canonical pathway present in plants, fungi and animals? Do other upstream modifications of prenyldiphosphats exist? With the non-canonical terpene biosynthesis a new research area was initiated!

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