Identification and characterization of a kunzeaol synthase from Thapsia garganica - DTU Orbit (17/01/2019)

Identification and characterization of a kunzeaol synthase from *Thapsia garganica*: implications for the biosynthesis of the pharmaceutical thapsigargin

Thapsigargin is a major terpenoid constituent of *Thapsia garganica* root. Owing to its potent antagonistic effect on the sarcoplasmic/endoplasmic reticulum Ca$^{2+}$-ATPase, thapsigargin has been widely used to study Ca$^{2+}$ signalling and is also a potential drug for prostate cancer. Despite its importance, thapsigargin biosynthesis in *T. garganica* remains unknown. In order to decipher thapsigargin biosynthesis, deep transcript sequencing (454 and Illumina) of the *T. garganica* root was performed, and two terpene synthases (TgTPS1/2) were identified. Functional characterization of their encoded enzymes in a metabolically engineered yeast revealed that TgTPS1 synthesized delta-cadinene, whereas TgTPS2 produced ten distinct terpenoids. However, cultivation of the TgTPS2-expressing yeast in pH-maintained conditions (pH 6-7) yielded one major oxygenated sesquiterpenoid, suggesting that formation of multiple terpenoids was caused by acidity. The major terpene product from TgTPS2 was identified as 6β-hydroxygermacra-1(10),4-diene (kunzeaol) by mass-fragmentation pattern, retention index, the nature of its acid-induced degradation and NMR. Also, recombinant TgTPS2 efficiently catalysed the synthesis of kunzeaol *in vitro* from farnesyl diphosphate with a $K_m$ of 2.6 μM and a $k_{cat}$ of 0.03 s$^{-1}$. The present paper is the first report of a kunzeaol synthase, and a mechanism for the transformation of kunzeaol into the thapsigargin backbone is proposed.

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