



Engineering of *Corynebacterium glutamicum* towards increased malonyl-CoA availability for polyketide synthesis

Lars Milke

Schlüsseltechnologien / Key Technologies

Band / Volume 223

ISBN 978-3-95806-480-5

Forschungszentrum Jülich GmbH
Institut für Bio- und Geowissenschaften
Biotechnologie (IBG-1)

Engineering of *Corynebacterium glutamicum* towards increased malonyl-CoA availability for polyketide synthesis

Lars Milke

Schriften des Forschungszentrums Jülich
Reihe Schlüsseltechnologien / Key Technologies

Band / Volume 223

ISSN 1866-1807

ISBN 978-3-95806-480-5

Table of contents

Abstract.....	VI
Zusammenfassung.....	VII
Abbreviations	VIII
1 Scientific context and key results of this thesis.....	1
1.1 Polyketides – a highly diverse group of natural products with pharmacological relevance	1
1.2 Polyketide synthases	4
1.2.1 Type I polyketide synthases are large multi-domain enzymes.....	4
1.2.2 Small but versatile – type III polyketide synthases	4
1.3 Access to polyketides	8
1.4 Current status of microbial polyketide synthesis.....	8
1.5 <i>Corynebacterium glutamicum</i> – a promising host for polyketide synthesis?	11
1.5.1 Industrial relevance of <i>C. glutamicum</i>	11
1.5.2 Malonyl-CoA-dependent synthesis of polyphenolic polyketides with <i>C. glutamicum</i>	12
1.6 Aims of this thesis.....	15
1.7 Key results on engineering <i>C. glutamicum</i> for increased malonyl-CoA availability for polyketide synthesis.....	15
1.7.1 Increasing acetyl-CoA supply is essential for improving intracellular malonyl-CoA availability	15
1.7.2 Increasing ACC activity through modulation of FasR-mediated gene regulation improves malonyl-CoA availability.....	19
1.7.3 <i>C. glutamicum</i> as a microbial host for the synthesis of the pentaketide noreugenin.....	21
1.7.4 <i>C. glutamicum</i> as a microbial host for the synthesis of the phenylbutanoids raspberry ketone, zingerone and benzylacetone	24
1.7.5 <i>C. glutamicum</i> as a microbial host for the synthesis of the type I polyketide 6-methylsalicylic acid	27
1.8 Conclusion and outlook.....	28
2 Peer-reviewed publications.....	31
2.1 Limitations for the microbial synthesis of plant polyphenolic polyketides	31
2.2 Engineering <i>C. glutamicum</i> towards increased malonyl-CoA availability for plant polyphenol synthesis	42
2.3 Increasing malonyl-CoA availability for improved noreugenin synthesis.....	54
2.3.1 Supplementary Material	66

2.4	<i>C. glutamicum</i> is a promising host for the synthesis of type I polyketides	69
2.4.1	Supplementary material	82
2.5	Synthesis of flavoring phenylbutanoids with <i>C. glutamicum</i>	86
2.5.1	Supplementary material	98
3	References	104
4	Appendix	114
4.1	Author Contributions	114
4.2	Patent application	115
5	Danksagung	116
6	Erklärung	117

Schlüsseltechnologien / Key Technologies
Band / Volume 223
ISBN 978-3-95806-480-5