Heterologous production of immunosuppressant mycophenolic acid in Aspergillus nidulans

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Filamentous fungi are well-known producers of a wide range of valuable secondary metabolites, which can be advantageously exploited e.g. in the pharmaceutical industry. One of the most prominent examples is mycophenolic acid (MPA). MPA inhibits inosine-5'-monophosphate dehydrogenase (IMPDH), which catalyzes the rate limiting step in the guanine nucleotide synthesis. Since B- and T-lymphocytes rely entirely on de novo purine synthesis, MPA is used as an immunosuppressant during organ transplants. We have recently identified the mpa gene cluster in *Penicillium brevicompactum* [1] and have subsequently verified several steps in the MPA biosynthetic pathway [2,3,4]. However, the role of four genes remained to be characterized. We have therefore heterologously expressed the mpa cluster in a stepwise manner in *Aspergillus nidulans* and established a cell factory for MPA production. Using this strategy, we have demonstrated that MpaA possesses prenyl transferase activity and catalyzes the conversion from 5,7-dihydroxy-4-methylphthalide to 6-farnesyl-5,7-dihydroxy-4-methylphthalide (FDHMP). We have also shown that MpaG catalyzes the last enzymatic step in the biosynthesis of MPA in vivo, resulting in the production of MPA. Interestingly, one of the intermediates (demethyl-MPA) can be formed from FDHMP via an unknown enzymatic activity present in *A. nidulans*. Lastly, we also found exciting examples of cross chemistry in *A. nidulans*, which resulted in the production of MPA variants. In conclusion, we have successfully characterized the biosynthetic pathway of the top-selling drug, MPA and we have demonstrated that *A. nidulans* is a suitable cell factory for its heterologous production.