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Engineering the spatial organization of metabolic pathways

One of the goals of metabolic engineering is to optimize the production of valuable metabolites in cell factories. In this context, modulating the gene expression and activity of enzymes are tools that have been extensively used. Another approach that is gaining interest is the engineering of the spatial organization of biosynthetic pathways. Several natural systems for ensuring optimal spatial arrangement of biosynthetic enzymes exist. Sequentially acting enzymes can for example be positioned in close proximity by attachment to cellular structures, up-concentration in membrane enclosed organelles or assembly into large complexes. The vision is that by positioning sequentially acting enzymes in close proximity, the cell can accelerate reaction rates and thereby prevent loss of intermediates through diffusion, degradation or competing pathways. The production of valuable metabolites in cell factories does however often depend on both heterologous and host enzymes. In this case, no spatial coordination of the biosynthetic enzymes can be expected to be in place. Presumably this contributes to the low productivity regularly observed for heterologous pathways. In one test case, we investigated whether a heterologous pathway could be optimized by positioning two sequentially acting enzymes in close proximity. More specifically, we fused a sesquiterpene synthase of plant origin to a natural yeast enzyme and expressed it in the well-characterised cell factory *Saccharomyces cerevisiae*. Successfully, the sesquiterpene production was increased two-fold when the enzymes were fused

compared to when they were expressed from the same promoters as free enzymes. Moreover, the strategy could be used in combination with other traditional metabolic engineering strategies to increase the production of a desired product, as enzyme fusion combined with down-regulation of a competing pathway and up-regulation of a selected pathway enzyme resulted in a five-fold higher sesquiterpene production. This simple test case demonstrates that engineering of the spatial organization of pathways has great potential for diverting flux towards a desired product.