Meta-synthetic metabolism: Identification of critical intermediates for synthetic amino acid derivative production

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The growing catalogue of known enzymes gives promise for creating new useful biological products by combining transgenes in vivo and engineering enzymes with novel catalytic capabilities [1, 2]. Amino acid production is part of the core metabolism of every free-living organism, but derivatives of the standard 20 amino acids are often produced as part of the 'secondary metabolism.' For example, many neurotransmitters are derivatives of standard amino acids, and therefore amino acid derivatives are rich targets for drug discovery. Toward engineering cell factories for the production of useful amino acid derivatives, we have explored the potential catalytic space of known enzymatic functions.

We began with the rich set of more than 11,000 amino acid-like compounds in the PubChem database [3], and using these as target molecules, calculated acceptable metabolic pathways for their synthesis from glucose. For this we used the annotated enzymes from the KEGG database [4], and identified reaction steps between compounds that are currently present in nature, along with enzymatic steps which might be easily engineered due to high chemical similarity between known and target compounds. We scored each reaction step by chemical similarity (with 1 being a known reaction in KEGG), and used these to rank the pathways for producing each of more than 3,000 compounds with identified synthetic pathways.

From the calculated synthetic pathways, we found several compounds which acted as 'critical intermediates' which participated in more than 15 reaction steps. These compounds act as intermediates in the synthesis of multiple identified amino acid derivatives. We also found many amino acid derivatives which could be synthesized by only a single reaction pathway, relying on a unique enzyme from KEGG for the critical reaction step. Along with these results, we present some of the interesting amino acids identified from the study, along with possible applications in industry.

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