

Trace element associated reduction of norleucine and norvaline accumulation during oxygen limitation in a recombinant *Escherichia coli* fermentation.

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Abstract

Norleucine and norvaline belong to a group of non-canonical amino acids which are synthesized as byproducts in the branched chain amino acid metabolism of *Escherichia coli*. The earlier observed misincorporation of these rare amino acids into recombinant proteins has attracted increasing attention due to the rising use of protein based biopharmaceuticals in clinical application. Experimental data revealed pyruvate overflow inducing conditions, which typically occur in oxygen limited zones of large-scale fermentations as a major reason leading to norvaline and norleucine synthesis during *E. coli* cultivation. Previous approaches to suppress misincorporation of norleucine and norvaline considered growth media supplementation with the relevant canonical isostructural compounds, but no research was performed on the impact of the

overflow metabolism related trace elements molybdenum, nickel and selenium. These elements form essential parts of the formate hydrogen lyase (FHL) metalloprotein complex, which is a key enzyme of anaerobic pyruvate metabolism in *E. coli* and could therefore represent a crucial connection to the pyruvate accumulation associated biosynthesis of rare amino acids.

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