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Relationships between metabolic fluxes and enzyme amino acid composition

Research Article

Inara Kampenusa, Peteris Zikmanis*

Institute of Microbiology and Biotechnology, University of Latvia, LV-1010 Riga, Latvia

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Abstract: Metabolic fluxes are a key parameter of metabolic pathways being closely related to the kinetic properties of enzymes and could be conditional on their sequence characteristics. This study examines possible relationships between the metabolic fluxes and the amino acid (AA) composition (AAC) for enzymes from the yeast *Saccharomyces cerevisiae* glycolysis pathway. Metabolic fluxes were quantified by the COPASI tool using the kinetic models of Hynne and Teusink at 25 mM, 50 mM, and 100 mM of external glucose or employing literature data for cognate kinetic or stoichiometric models. The enzyme sequences were taken from the UniProtKB, and the AAC computed by the ExPASy/ProtParam tool. Multiple linear regressions (89.07% < R2 adjusted < 91.82%; P<0.00001) were found between the values of metabolic fluxes and the selected sets of AA frequencies (5 to 7 for each model). Selected AA differed from the rest by their physicochemical and structural propensities, thus suggesting a distinctive contribution to the properties of enzymes, and hence the metabolic fluxes. The results provide evidence that metabolic fluxes of the yeast glycolysis pathway are closely related to the AAC of relevant enzymes and support the view that catalytic, binding and structural residues are interdependent to ensure the efficiency of biocatalysts.

Keywords: *Saccharomyces cerevisiae* • *Metabolic fluxes* • *Glycolytic enzymes* • *Amino acid composition* • *Multivariate relationships*

Abbreviations

AA - amino acid;
AAC - amino acid composition;
LOOCV - leave-one-out cross-validation;
VIF - variance inflation factor.

1. Introduction

Cell metabolism is comprised of enzyme-catalyzed biochemical reactions and carrier-mediated transport processes. Taken as a whole, these reactions form interrelated metabolic pathways which are combined into a cellular metabolic network. Metabolic fluxes describe the amount of material chemically converted or transported per time unit and are considered as the key parameters of any metabolic pathway and hence, as the fundamental determinants of cell physiology [1-4]. Changes in metabolic fluxes in response to various types of genetic and environmental perturbations are critical for the metabolic flux control which is a key objective of metabolic engineering [5,6]. On the other hand, enzyme activity is one of the major factors influencing the magnitude of metabolic fluxes in any cell [6]. According to concepts of systems biology, metabolic fluxes are net sums of underlying enzymatic reaction rates represented by integral outputs of three biological quantities which interact at the level of enzyme kinetics: kinetic parameters, enzyme and reactant concentrations [7]. An integrated view on enzymes suggests them as dynamic assemblies whose variable structures are closely related to catalytic functions [8,9]. It is therefore important to extend our knowledge of enzyme sequence, structure, and function relationships [10], as well as to explore coherencies between enzyme activity profiles and metabolic flux distributions in order to understand the physiological dynamics within a cell [2,11].

Amino acid (AA) composition (AAC) is a simplest attribute of proteins among so-called global sequence

* *E-mail: zikmanis@lanet.lv*