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High-Throughput Kinetic Screening of Non-Enzymatic Metabolic Conversions Driven by Single Amino Acids

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Introduction: Modern metabolism is organized in a set of highly efficient pathways catalyzed by enzymes. However, it is increasingly acknowledged that a variety of spontaneous, non-enzymatic reactions occur concomitantly with enzyme functions, recalling the relics of an ancestral remote network governed by very rudimentary activities. What were the structural and kinetic properties of those systems and how could they have progressed towards more efficient biological networks?

Results: In this work we explore the combined catalytic potential of single amino acids and metals on intermediates of central carbon metabolism. We make use of quantitative metabolomics techniques in enzyme-free *in vitro* assays to reconstruct the reactivity landscape and kinetics of what are regarded as some ancestral pathways. An unbiased high-throughput screening for catalytic individual amino acids was performed on more than 200 possible reactions among sugars from glycolysis and pentose phosphate pathway. Cysteine turned out to be a prominent enhancer of several interconversions between sugar phosphates. Moreover, these effects were further improved by metal ions, in particular iron (II). We provide structural and dynamical evidences (based on NMR and LC/MS data, respectively) of complementarity between these molecules. Through this illustrative example we would like to highlight the benefits of a metal-amino acid alliance and show some specificity/efficiency issues during the first evolutionary steps towards enzyme catalysis.