



The widespread role of non-enzymatic reactions in cellular metabolism

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Enzymes shape cellular metabolism, are regulated, fast, and for most cases specific. Enzymes do not however prevent the parallel occurrence of non-enzymatic reactions. Non-enzymatic reactions were important for the evolution of metabolic pathways, but are retained as part of the modern metabolic network. They divide into unspecific chemical reactivity and specific reactions that occur either exclusively non-enzymatically as part of the metabolic network, or in parallel to existing enzyme functions. Non-enzymatic reactions resemble catalytic mechanisms as found in all major enzyme classes and occur spontaneously, small molecule (e.g. metal-) catalyzed or light-induced. The frequent occurrence of non-enzymatic reactions impacts on stability and metabolic network structure, and has thus to be considered in the context of metabolic disease, network modeling, biotechnology and drug design.

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Introduction

The metabolic network originates from a low number (or one) of ancestral forms, and all living organisms share core reaction sequences and structural properties in their metabolic networks [1]. Glycolysis and gluconeogenesis, pentose phosphate pathway (PPP) and tricarboxylic acid (TCA) cycle are central metabolic pathways and exemplary for the conservation of metabolism [2,3]. Their products glucose, pyruvate, ribose-5-phosphate and erythrose-4-phosphate are common precursors for amino acids, lipids and nucleotides. Despite the high level of conservation of

the reactions, the participating enzymes have however multiple origins. Sequences of glycolytic enzymes differ between Archaea and Bacteria/Eukaryotes [2,4,5]. This divergence can be explained by both, independent evolutionary origins of enzymes and stepwise replacement of ancestral enzymes by modern forms [5]. Both scenarios require an initial reaction sequence as ‘template’, as evolution can only select for a functional product (‘end-product problem’ [6]). The initial metabolic pathway can thus either evolve backward from the advantageous end-product (retro-evolution), provided that precursors are formed non-enzymatically [6], or by improving a non-enzymatic reaction sequence starting from its most rate-limiting step [7]. A plausible primordial base can be traced for glycolysis and the PPP, as several of their reactions can be replicated with metal catalysts, in particular Fe(II), under conditions reproducing the ocean chemistry of the Archean world [8]. Fe(II) was broadly available before oxygenation of the early Earth [9], implying a scenario for the first glycolytic enzymes being simple iron-binding RNA or oligopeptide molecules, which would have possessed the potential of enhancing many reactions now found in central metabolism [7,8] (Box 1).

Three classes of non-enzymatic reactions contribute to modern cellular metabolism

It is important to emphasize that the same thermodynamic principles apply for non-enzymatic and enzymatic reactions, and every enzymatic reaction can occur in principle also non-enzymatically [10]. Non-enzymatic reactivity of metabolites is a well-known phenomenon since the beginning of enzymology (Figure 1a). However, network topologies or genome-scale metabolic models were not prevailing research questions until the event of Systems Biology, and until recently for many cases the metabolic role of non-enzymatic reactions obtained little attention.

The presence of enzymes does not prevent non-enzymatic reactions to occur across the metabolic landscape. On the basis of their principal mode of action, we divide non-enzymatic reactions into three classes (Figure 1b): Class I reactions present broad chemical reactivity and low specificity. These include Maillard-reactions, a conjugation of amino group-containing compounds (e.g. amino acids) and sugars [11], oxidation reactions driven by reactive oxygen species (ROS) and non-enzymatic covalent modifications of lipids and proteins (alkylation, glycosylation and acetylation) [12]. These indiscriminate reactions are not the main focus of this review; nonetheless, they have a strong

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Box 1 Evolutionary replacement of metal catalysis with protein catalysts: the case of ribulose 5-phosphate 3-epimerase, which exists as an Fe(II)-dependent form and an iron-independent form. While in many bacteria the Fe(II)-dependent form dominates, in higher eukaryotes it is the iron independent form [69]. As the isomerization of ribulose 5-phosphate is catalyzed by Fe(II) also in the absence of the enzyme [8] indicates that the iron-dependent form is the older enzyme. Exchanging the Fe(II)-dependent with the metal-independent form of the epimerase does provide selective advantage: the Fe(II) catalyst in the bacterial epimerase gets readily oxidized, in fact this enzyme is the first one damaged when *Escherichia coli* is exposed to oxidants; the Fe(II) dependence of RPE is thus one major cause why *E. coli* cells can tolerate only moderate H_2O_2 levels [70].

effect on cellular physiology and are important driving forces for evolution.

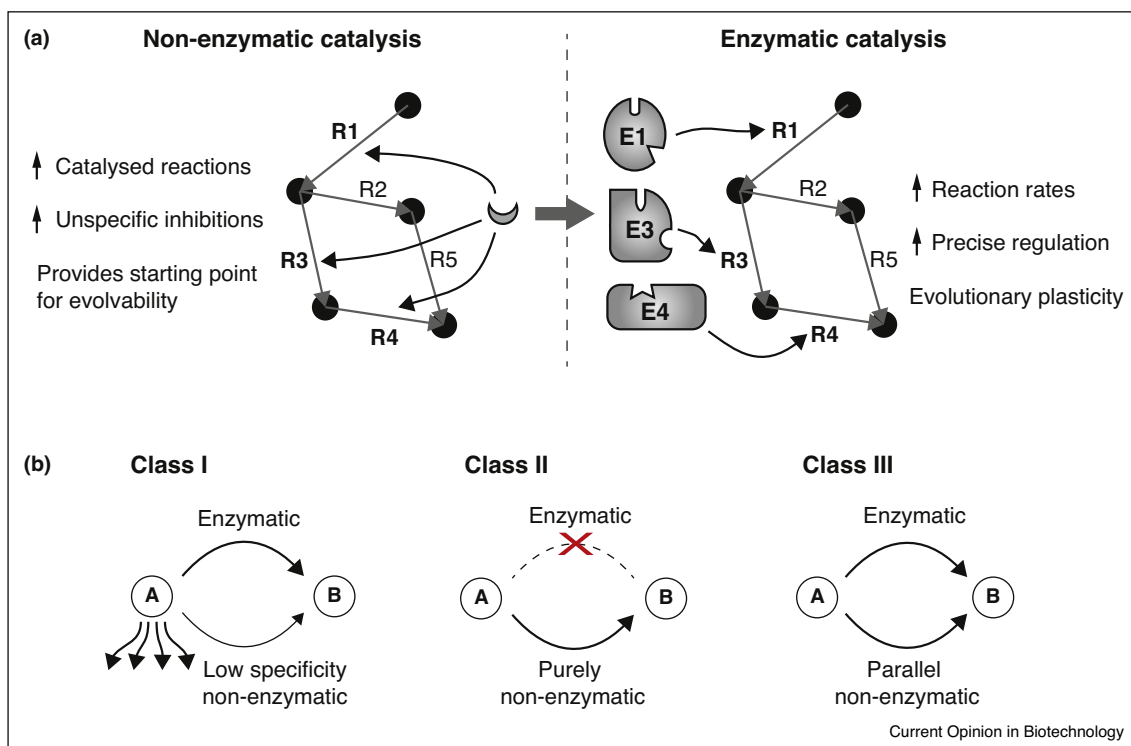
Other non-enzymatic reactions are highly specific and are integral part of the metabolic network. Class II reactions occur purely non-enzymatically. A well-known example is the maturation of vitamin D_3 where a precursor is transported to the skin, to be converted by UV light to previtamin D_3 [13^{*}]. Most Class II reactions are spontaneous reactions which do not depend on a catalyst or an atypical

energy source, such as the next downstream reaction in vitamin D_3 biosynthesis, in which previtamin D_3 undergoes spontaneous isomerization forming vitamin D_3 [13^{*}].

Class III non-enzymatic reactions occur parallel to enzyme functions. Class III reactions are widespread in metabolism, and indicate that many metabolic pathways descend from promiscuous or non-enzymatic precursors. Frequently, the parallel enzyme operates to prevent unwanted secondary products that would be generated in the non-enzymatic reaction (negative catalysis). Examples include the spontaneous transamination of glyoxylic acid and amino acids [14], the isomerization of propyl residues [15], the decarboxylation of aminomalonic acid [16] and the formation of oxysterols from cholesterol [17]. Class III non-enzymatic reactions occur analogous to all six major enzymatic classes, illustrated for the following examples:

- (i) *Oxidoreductases*: catalase (Figures 2 and 3a). Hydrogen peroxide (H_2O_2) is formed as a (by-)product in various redox reactions. In combination with Fenton chemistry, H_2O_2 can react into superoxide and damage proteins, RNA, DNA and lipids [18].

Figure 1



Non-enzymatic reactions in cellular metabolism. (a) *Evolution*. Non-enzymatic reactions (R1, R3, R4, left panel) provide a template for the evolutionary selection of enzymes (E1, E3, E4). Enzymes can achieve higher substrate specificity and reaction rate, can be regulated and decrease the dependency on rare catalysts. (b) *Three classes of non-enzymatic reactions dominate in modern metabolism*. The presence of enzymes does not prevent or replace non-enzymatic metabolic reactions, which divide into three classes: Class I reactions are non-specific and act on a broad range of substrates, Class II reactions are specific and occur exclusively non-enzymatic as part of the metabolic network, while Class III reactions occur simultaneously in an enzymatic and non-enzymatic manner.

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