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Relationship between topology and functions in chloroplast metabolic network evolution



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Short Abstract: We found the enzymes in the highly conserved functional pathways and modules are highly connected and the relationship between topology and functions is very similar in metabolic networks of chloroplast and cyanobacteria, while different from other species. The relationship can be used as an indicator of the closeness in evolution.

Long Abstract:

The preferential attachment model was suggested as a generic network evolution model that yields the universal scale-free property, where new nodes are more likely to connect to well-connected nodes in the network [1]. Recently Light S et al. found the evidence for preferential attachment in the metabolic network evolution of *E. coli* [2]. What is the relationship between the topological connections among enzymes and their functions? Does this relationship exhibit similarity between evolutionarily close related organisms? Here we focus on the analysis of chloroplast metabolic networks and comparison with those of cyanobacteria to explore the conservation and changes during endosymbiosis.

In our previous study, we have reconstructed metabolic networks of chloroplast and cyanobacteria, and compared the overall topological properties and modular structures between them, which demonstrated that, all cyanobacteria exhibit very similar properties, while chloroplast is overall less dense and more modular [3]. Therefore, we only choose one cyanobacteria *Synechococcus* sp. WH8102 (syw) as a representative in this study. We also included *E. coli*, *Arabidopsis thaliana* and *Cyanidioschyzon merolae* in the comparison. We further analyzed enzyme connectivity and its relation with pathway function, enzyme classification, functional modules and horizontal gene transfer.

The average connectivity of all enzymes in chloroplast and syw is 14.77 and 17.61 respectively. Two hundred and ten enzymes are shared with average connectivity of 17 in chloroplast and 20 in syw. Among the not shared enzymes, the average connectivity is 12 and 14 respectively, which is much lower than that of the shared parts. We then compared the k-core of the two networks. In chloroplast, the largest core includes 32 enzymes and each has at least 28 neighbors; in syw, 37 enzymes and 31 neighbors. The average connectivity of enzymes in these two cores is 42.41 and 48.22 respectively, which are higher than the other cores of the networks. We also classified the enzymes into nine major functional pathways according to KEGG. The mean connectivity for enzymes involved in amino acid metabolism, nucleotide metabolism, and energy metabolism are higher in all species in this study. People believe that enzymes in these elementary metabolic processes are relative older and more conservative [2]. The high connectivity of these enzymes showed

in our study supports preferential attachment. In contrast, enzymes involved in lipid and glycan metabolism are relatively less connected. Among all the pathways existed in chloroplast, we found that the average connectivity is very similar between chloroplast and syw, but very different from other species. Next, we examined the association between enzyme classification and connectivity. The average connectivity of synthetases is the highest in all species examined followed by transferases and lyases. The two least connected enzyme classes are hydrolases and isomerases. Across species, we found again that the average connectivity of each enzyme classification is very similar between chloroplast and syw. In our previous study on modularization of networks, we found five pairs of modules with very similar enzyme contents in chloroplast and syw, among which three pairs mainly correspond to amino-acid metabolism, and the other two pairs belong to nucleotide metabolism and carbohydrate metabolism respectively [3]. Here we rank the modules by average connectivity and found most of highly connected enzyme nodes exist in conserved modules between these two species. For example, the top three modules with high connectivity in chloroplast and syw are the best matches to each other, which mainly consist of enzymes related to amino-acid metabolism.

Furthermore, we explore if the connectivity of horizontal transferred enzymes (HGT enzymes) differs from others. We obtained 49 chloroplast enzymes that are likely transferred from cyanobacteria [4]. The average connectivity of these HGT enzymes is 19.3, while the other enzymes have an average connectivity of 14.1. In addition, 88% of the HGT enzymes exist in the conserved modules corresponding to elementary metabolism. The slightly higher connectivity of HGT enzymes suggested that horizontally transferred genes are introduced and retained preferentially at central positions of the metabolism in chloroplast. In addition, we found 11 isozymes in chloroplast. The mean connectivity for the isozymes and non-isozymes is 30.82 and 14.29 respectively. Similarly, there are 18 isozymes in syw, and the average connectivity is 26.78 and 17.14 respectively for isozymes and non-isozymes. The occurrence and evolution of isozymes follow patchwork pattern. They originated from common enzyme initially having broad specificity and then evolved to specialized enzymes with similar structure and function. Moreover the significant high connectivity of isozymes demonstrated that patchwork theory and preferential attachment drive the pathway and network evolution at different levels.

In conclusion, the enzymes in the highly conserved functional pathways and modules such as amino acid metabolism, nucleotide metabolism and carbohydrate metabolism are highly connected comparing to other modules. Our findings support the preferential attachment model. Despite the drastic re-organization of metabolism in chloroplast during endosymbiosis, the relationship between topology and functions is very similar between chloroplast and its precursor cyanobacteria, which demonstrate that the relationship can be used as an indicator of the closeness in evolution.

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