Rare Sugars: Applications and Enzymatic Production

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Rare sugars are monosaccharides and their derivatives rarely existing in nature. Of all hexoses and pentoses, only seven (D-glucose, D-galactose, D-mannose, D-fructose, D-xylene, D-ribbose and L-arabinose) are present in significant amounts in nature. Despite their low natural abundance, rare sugars have various known biological functions and enormous potential for applications in pharmaceutical, cosmetics, food and flavour industries [1-4]. For example, D-tagatose is a low-calorie sweetener used in food, beverage and diet supplement [5,6]. It was approved as a food additive by the FDA in 2003. Recently D-tagatose has also been proved to be a potentially important drug for treating type 2 diabetes [7,8]. L-nucleoside analogues show increased antiviral activity and good metabolic stability. Some rare sugars are used as building blocks to synthesize the nucleoside analogues which are used as antiviral and anticancer agents [9]. For example, L-ribose, the enantiomer of D-ribose, is used to prepare clevudine, an antihypertension B virus drug [10,11]. L-xylene is used to synthesize 9-(2-deoxy-2-fluro-b-L-arabinofuranosyl) pyrimidine nucleosides with anti-hepatitis B virus activity [12]. L-gulose and L-galactose can also be used to produce L-nucleosides [13,14]. D-allose has attracted much attention in recent years due to its various biological functions such as anti-tumor, anti-inflammatory, anti-oxidative and immunosuppressant activities [15]. Rare sugars can also be used as starting materials to synthesize other valuable compounds. For example, D-arabinose is used to synthesize antitumor compounds, such as dehydroamino acid derivatives [16,17].

Because rare sugars occur only in small amounts in nature, their properties have not been fully studied. The research of their synthesis becomes important because it will lead to further evaluation and application of rare sugars. Carbohydrates contain multiple chiral carbons, so their chemical synthesis processes are tedious and time-consuming. The enzyme approach is particular powerful in carbohydrate synthesis due to the high stereospecificity of enzyme catalysis. Prof. Ken Izumori from Kagawa University developed the strategies for preparing all hexoses from the inexpensive sugar glucose [18,19]. In Izumoring strategy, the interconversion of monosaccharides is realized by oxidoreductases, aldose isomerasers, D-tagatose 3-epimerase and aldose reductases. The synthesis route of a target rare sugar can be easily designed according to Izumoring strategy. The Izumoring strategy was further updated by adding synthesis strategies of pentoses by Beerens et al. [20]. However, because rare sugars are unnecessary for organisms, in many cases they are the minor products of the enzyme reactions, which implicates that the production of rare sugars is not high enough and can be further improved by enhancing the catalysis efficiency of the enzymes. For example, the D-tagatose manufacturing process includes galactose isomerization by L-arabinose isomerase. As galactose is not the most efficient substrate for L-arabinose isomerase, the yield of D-tagatose needs to be further improved by engineering the substrate binding pocket of the enzyme [21]. In order to produce substantial quantities of rare sugars for further evaluation of their properties or for new applications discovery, the relatively low activities of their synthetic enzymes need to be engineered.

Directed evolution strategies have been proved to be a powerful tool in enhancing the activity or substrate selectivity of various enzymes. It has also been applied in rare sugar synthetic enzyme engineering. Directed evolution of L-arabinose isomerase has yielded the enzyme mutant with 68% increase in isomerization activity for D-galactose [22]. Engineering the recombining NAD-dependent mannotol-1-dehydrogenase from Apium graveolens with random mutagenesis method has improved the thermal stability of this enzyme and thereby improved the production of L-gulose and L-galactose from D-sorbitol and galactitol, respectively [13]. However, so far directed evolution strategy has not been widely used in improving rare sugar production. Engineering enzymes in rare sugar synthesis routes to improve the yield of the rare sugars will become the next important field in rare sugar study.

References


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Received: September 17, 2012 Accepted: September 19, 2012 Published: September 24, 2012

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