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REVIEW

Recent Progresses in Molecule Motors Driven by Enzymatic Reactions

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Abstract: It is traditionally assumed that enzymatic reaction does not perturb the diffusion of an enzyme itself. Recent studies showed that the diffusivity of enzymes increased in a substrate-dependent manner during catalysis. Thus, the energy released during enzyme catalysis could be used to propel nanoscale objects, e.g. molecule motors driven by enzymatic reactions. Although the dependence of enzyme diffusion on substrate has been reported in several different enzyme systems, the exact origin of this phenomenon is still unknown yet. However, several possible mechanisms were proposed for the enhanced diffusion. This review illustrates recent progress in the research on the influence of enzymatic reaction on the diffusivity of enzymes, including the change of diffusion coefficient of enzymes, potential mechanisms and related applications.

Key Words: Enzymatic reaction; Diffusion coefficient; Chemotaxis; Self-propelled; Nanomotor; Review

1 Introduction

Brownian motion is the random motion of particles suspended in liquid resulting from collision with the quick atoms or molecules. Enzyme molecules in solution diffuse randomly in the absence of substrate (Brownian motion). However, in the presence of substrate, enzyme could catalyze substrate turnover and release chemical free energy. It is traditionally assumed that the free energy released by a turnover event doesn't perturb enzymes[1]. However, recent studies have shown that the diffusivity of enzymes increases in a substrate-dependent manner during catalytic reactions, and the diffusion coefficient increases with the increase of concentrations of correspongding substrate. Thus, enzyme molecules can propel the motion of themselves by using the released energy during enzymatic reactions.

Motors are natural or synthetic machines that generate mechanical forces and cause directional transport by consuming energy either from chemical fuels or from external sources[2]. Motion is an inextricable part of life, and a variety of chemically powered motors exist inherently in our body to sustain our life. In biological systems, enzyme-based biological motors perform specific cellular functions, such as DNA synthesis and vesicular transport, with great precision and efficiency[3–6]. In fact, there are various motors in organism, such as myosins, dyneins and kinesins, all of which are cytoplasmic motors and use ATP as energy source to achieve directional motion on certain tracks (e.g., microtubules). On a higher level, biological motors also facilitate the directed movement of cells toward specific chemicals or light[7,8]. In all cases above, these movements are results of harnessing chemical free energy released from enzyme catalyzed turnover of substrates. In living organisms, enzyme is one kind of biological catalysts that can catalyze various chemical reactions. In view of the diversity, high-efficiency of enzyme and that enzyme molecules can harness the energy released from substrate turnover to propel themselves, catalytic motors based on enzymes would greatly expand and enrich the strategies to power nano- and micromotors. In addition, if tethering these enzymatic systems

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to surface, the mechanical force transfer from enzymatic reaction can also power the movement of the enzymes themselves and that of nearby particles, as well as the pumping of the surrounding fluid[9]. This opens up a new avenue of designing novel stimuli-responsive autonomous drug-delivery system. In this article, the enhanced diffusion of enzymes during catalysis and the related applications in fabricating molecular motors are reviewed.

2 Diffusion of enzymes during enzymatic reactions

2.1 Influence of enzymatic reactions on the diffusion coefficient of enzyme

Recent studies have shown that the diffusion coefficient of enzyme increases with the increase of substrate concentration. In 2009, Schwartz's group from University of Wisconsin showed the first experimental evidence that a molecular complex consisting of a DNA template and associated RNA polymerases (RNAPs) displayed enhanced diffusion in the presence of its substances (NTPs), and the complex tended to move toward the area where the concentration of NTPs was high. This is a behavior similar to chemotaxis of organisms or cells[10], as shown in Fig.1.

Soon afterwards, Sen's group[11] from the Pennsylvania State University measured catalysis-enhanced diffusion of urease at single-molecule-scale (as shown in Fig.2), and calculated the force responsible for this enhancement using Brownian dynamics simulations (about 12 pN). Recent studies of Sen's group showed that the diffusivity of enzymes increased in a substrate-dependent manner. However, the exact mechanism for the enhanced diffusion is unclear yet. In 2015, Bustamante's group from University of California performed a series of experiments and a number of crucial controls about the diffusion behavior of four enzymes. They found that the enhanced diffusion of enzymes arose from the heat released from enzymatic reactions and only enzymes that catalyzed exothermic reactions displayed enhanced diffusion coefficient, which increased linearly with the reaction rate[1] (Fig.3). The enhanced diffusion of enzymes during catalytic reactions suggests that the released energy during catalytic turnover can be harnessed by the enzymes for self-propulsion. Thus, the influence of enzymcatic reaction on the enzyme itself should be reconsidered, which are of great significance to understand some behavior of enzymes during catalytic reactions.

2.2 Mechanism for enhanced diffusion of enzyme itself during enzymatic reaction

Even though recent studies have shown that the diffusion coefficient of single enzyme molecule increases in a substrate-dependent manner during catalysis, however, the exact mechanism for the enhanced diffusion of enzymes is not clear. In 2010, Sen's group proposed several possible mechanisms to explain the dependence of the enhanced diffusion of urease during the urea hydrolysis reaction[11]. One possible mechanism is that the generation of charged reaction products might result in an asymmetric electric field in vicinity of the enzyme, which induced an enhanced diffusion of the charged enzyme molecules. As in the case of urease-catalyzed reaction, because the diffusion coefficient of NH_4^+ ions is higher than those of the anions (HCO_3^- and HPO_4^{2-})

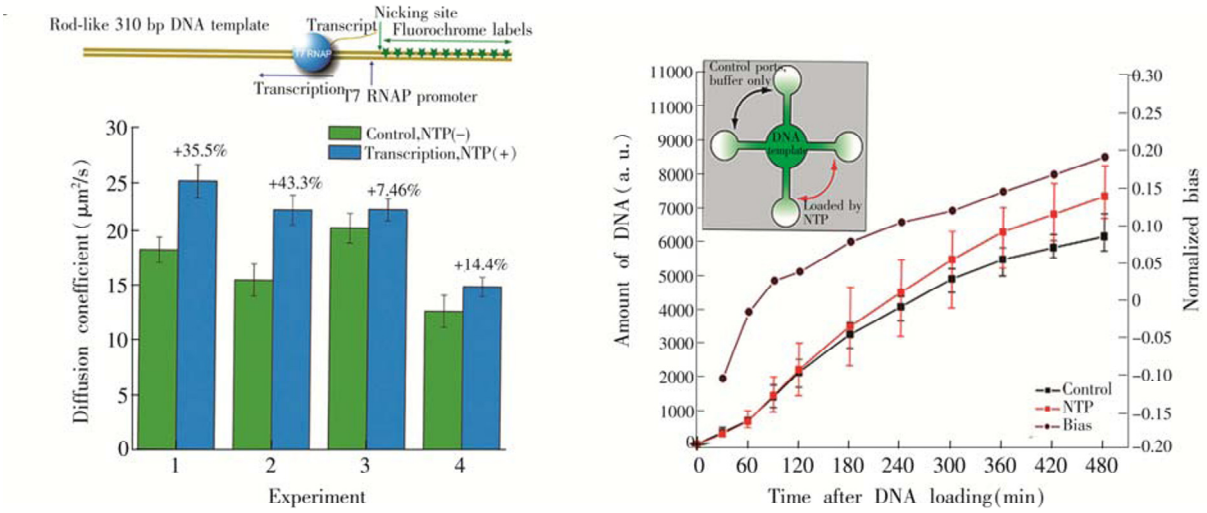

Fig.1 (A) Fluorescence recovery after photobleaching (FRAP) measurement of chemokinesis by T7 RNAP transcription. Error bar: standard deviation. Percentage increase in the apparent diffusion coefficient compared to Brownian diffusion is shown. (B) DNA chemotaxis: biased DNA transport toward NTP gradient. Error bar: range. Bias [normalized, $(F_{NTP} - F_{control})/F_{control}$; purple line] reveals enhanced DNA transport toward the NTP gradient, demonstrating DNA chemotaxis mediated by transcription. Reproduced with permission from Ref. [29], copyright © 2009, American Chemical Society