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DNA unwinding mechanism of helicases

Helicases are a class of proteins that are responsible for separating DNA duplex into single strands, which is a precursor to many types of DNA transactions in the cell. According to the structures, helicases fall broadly into two groups—non-hexameric and hexameric helicases. For the former group, a lot of in vitro experimental data showed that some are "inactive" in DNA unwinding in the form of monomer while others are "active" in the form of monomer. Here, it is proposed that although they show very different DNA unwinding activities, all helicases use the same mechanism to unwind DNA.

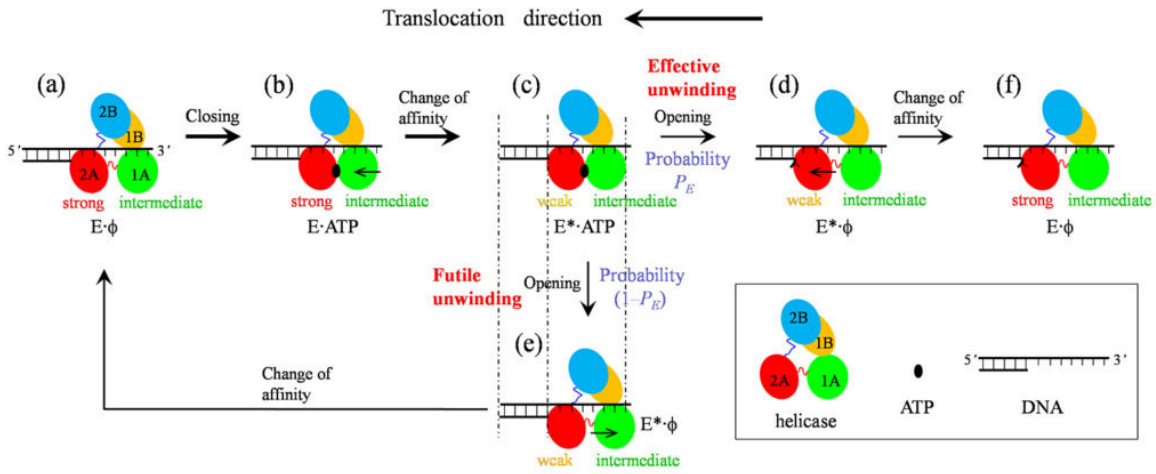

Fig. 1. Schematic of DNA unwinding mechanism of non-hexameric helicases.

We focus on non-hexameric helicases. Some consist of four domains (1A, 1B, 2A, 2B) while others have no the domain that is equivalent to 2B of the four-domain helicases. The mechanism is schematically shown in Fig. 1. We begin a chemomechanical coupling cycle with 2A binding strongly to single-stranded DNA (ssDNA) while 1A having an intermediate interaction with the ssDNA (Fig. 1a). ATP binding closes the cleft between 1A and 2A. Since now 2A binds strongly to the ssDNA, the cleft closing causes the movement of 1A along the ssDNA toward 2A (Fig. 1b). The cleft closing then induces the change in the affinity of 2A from strong to weak but with the affinity of 1A changing insensitively (Fig. 1c). After ATP hydrolysis, the release of ATP-hydrolysis products opens the cleft. Since now 2A has the weak interaction with the ssDNA, the cleft opening causes most probably the downstream movement of 2A along the ssDNA. In the presence of the downstream duplex, the downstream movement of 2A would cause DNA unwinding (with probability P_E) (Fig. 1d). However, the resistance resulting from the DNA unwinding would impede the downstream movement of 2A and thus the cleft opening would instead cause the upstream movement of 1A by overcoming the intermediate binding energy of 1A with the ssDNA (with probability $1–P_E$) (Fig. 1e). The cleft opening then induces the change in the affinity of 2A from weak to strong (Fig. 1f or a).

With Fig. 1, various in vitro experimental data of DNA unwinding velocity versus an external force applied to the ends of the DNA duplex to unzip the duplex can be explained quantitatively. In the mechanism,

different helicases have different values of that is defined as the difference between the intermediate affinity of 1A for the ssDNA and the weak affinity of 2A during the DNA unwinding step. For the helicase with a very small value of that gives $P_E << 1$, its unwinding activity is very weak in the monomeric form under no external force on the ends of DNA to unzip the duplex, behaving as "inactive" in the in vitro experiments; however, a large force can increase greatly the unwinding activity; and the great increase in unwinding activity in the dimeric form results mainly from the fact that the upstream helicase prevents 1A of the downstream helicase, which is bound to the ssDNA near the fork, from moving upstream during the DNA unwinding step, reducing greatly the futile unwinding probability $1–P_E$. By contrast, for the helicase with a large value of that gives a large P_E, its unwinding activity is high in the monomeric form even under no external force on the ends of DNA to unzip the duplex, behaving as "active" in the in vitro experiments; and a large force has insensitive effect on the unwinding activity.

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Publication

Dynamics of monomeric and hexameric helicases.
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Biophys Chem. 2016 Apr