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Review

Prokaryotic DNA Crossroads: Holliday Junction Formation and Resolution

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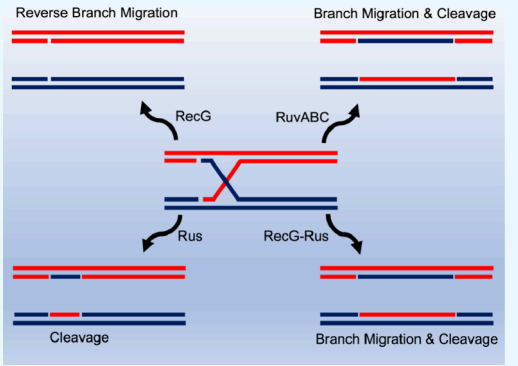
ABSTRACT: Cells are continually exposed to a multitude of internal and external stressors, which give rise to various types of DNA damage. To protect the integrity of their genetic material, cells are equipped with a repertoire of repair proteins that engage in various repair mechanisms, facilitated by intricate networks of protein−protein and protein−DNA interactions. Among these networks is the homologous recombination (HR) system, a molecular repair mechanism conserved in all three domains of life. On one hand, HR ensures high-fidelity, template-dependent DNA repair, while on the other hand, it results in the generation of combinatorial genetic variations through allelic exchange. Despite substantial progress in understanding this pathway in bacteria, yeast, and humans, several critical questions remain unanswered, including the molecular processes leading to the exchange of DNA segments, the coordination of protein binding, conformational switching during branch migration, and the resolution of Holliday Junctions (HJs). This Review delves into our current understanding of the HR pathway in bacteria, shedding light on the roles played by various proteins or their complexes at different stages of HR. In the first part of this Review, we provide a brief overview of the end resection processes and the strand-exchange reaction, offering a concise depiction of the mechanisms that culminate in the formation of HJs. In the latter half, we expound upon the alternative methods of branch migration and HJ resolution more comprehensively and holistically, considering the historical research timelines. Finally, when we consolidate our knowledge about HR within the broader context of genome replication and the emergence of resistant species, it becomes evident that the HR pathway is indispensable for the survival of bacteria in diverse ecological niches.



1. INTRODUCTION

Recombination is a vital component of DNA metabolism, leading to both high-fidelity, template-dependent repair and generation of combinatorial variations through allelic exchange, which bears significant evolutionary implications. This process is conserved across all three domains of life and plays a pivotal role in generating genetic diversity, preserving genome integrity, and ensuring the proper segregation of chromosomes. Despite substantial progress in understanding this pathway in bacteria, yeast, and humans, numerous essential questions remain unanswered. These include elucidating the molecular mechanisms driving the exchange of DNA segments, orchestrating protein binding, dynamics of conformational transitions in proteins and DNA during branch migration, and the resolution of Holliday Junctions (HJs). The occurrence of recombination was initially described in the bacterium *Escherichia coli* as "conjugation" in the mid-1940s by J. Lederberg and E. L. Tatum. For an in-depth exploration of these pioneering contributions to science, readers are referred to the literature.[1−7] These early studies provided compelling evidence for gene recombination in *E. coli*, suggested as a result of a sexual process analogous to that found in eukaryotes.[2,8] Subsequently, the isolation of recombination-deficient mutants of *E. coli* K12 and their abnormal responses to ultraviolet (UV)/X-rays/γ-rays supported the idea that genetic recombination also occurs during DNA repair events. Furthermore, it became evident that certain common enzymes serve roles in both genetic recombination and repair after irradiation.[9−12] A minimum of 11 rec mutants were identified in *E. coli*, each with approximate map locations. These mutants displayed distinctive traits, including reduced recombinant formation in specific genetic contexts and minimal to no impact on plasmid inheritance. Moreover, a number of *uvr* (*uvrA-uvrD*) and *dna* (*dnaA-dnaG*) mutants emerged, which exhibited sensitivity to UV irradiation and a conditional block in DNA synthesis, although they did not experience a decrease in recombination frequency.[13−15] Virtually all the *rec* genes identified encode proteins that function individually or through a complex

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