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Review

The DNA trackwalkers: Principles of lesion search and recognition by DNA glycosylases☆

Dmitry O. Zharkov[a,b,*], Arthur P. Grollman[c,*]

[a] *Laboratory of Repair Enzymes, SB RAS Institute of Chemical Biology and Fundamental Medicine, Novosibirsk 630090, Russia*
[b] *Novosibirsk State University, Novosibirsk 630090, Russia*
[c] *Laboratory of Chemical Biology, Department of Pharmacological Sciences, Stony Brook University, Stony Brook, NY 11794, USA*

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Abstract

DNA glycosylases, the pivotal enzymes in base excision repair, are faced with the difficult task of recognizing their substrates in a large excess of unmodified DNA. We present here a kinetic analysis of DNA glycosylase substrate specificity, based on the probability of error. This novel approach to this subject explains many features of DNA surveillance and catalysis of lesion excision by DNA glycosylases. This approach also is applicable to the general issue of substrate specificity. We discuss determinants of substrate specificity in damaged DNA and in the enzyme, as well as methods by which these determinants can be identified.

Keywords: DNA repair; DNA glycosylases; Substrate specificity; One-dimensional sliding; Protein dynamics

Contents

Abbreviations: 1D, 3D, one-, three-dimensional; 8-oxoG, 8-oxodG, 8-oxoguanine, 8-oxo-2′-deoxyguanosine; AP, abasic (site); BER, base excision repair; DHU, dihydrouracil; dsDNA, double-stranded DNA; Fapy-A, Fapy-G, formamidopyrimidine derivatives of A and G, respectively; GCS, general chemical space; QSAR, quantitative structure–activity relationship; RLS, relevant ligand set; ssDNA, single-stranded DNA

☆ Unless otherwise specified, bacterial enzymes discussed in this paper (designated according to the convention for prokaryotes, e.g., Ung or Fpg) are from *E. coli* and eukaryotic enzymes (designated by all capital letters, e.g., UNG or OGG1) are from *H. sapiens*.

* Corresponding authors.
E-mail addresses: dzharkov@niboch.nsc.ru (D.O. Zharkov), apg@pharm.stonybrook.edu (A.P. Grollman).

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Prologue

A little more than a decade ago, my longstanding interest in chemical biology led me to wonder, as did Phil Hanawalt, how DNA repair enzymes found their cognate lesions in a sea of undamaged DNA. In 1965, Hanawalt (with Bob Haynes) had proposed a model to explain damage recognition (see Hanawalt, PC, "Close-fitting sleeves"—Recognition of structural defects in duplex DNA, Mut. Res., 289 (1993) 7–15). Although we had never met, I appreciated the value of spending part of my sabbatical leave in Phil's laboratory, pondering this seminal question of recognition. While in residence at Stanford, I regularly visited the Computer Graphics laboratory at UCSF headed by Robert Langridge, where I learned (from Teri Klein) the essentials of molecular modeling. Despite his seemingly being impressed when I demonstrated this powerful approach, Phil clearly did not require such technology to formulate models for damage recognition, preferring to use his own brain for 3D-conceptual processes. In fact, the "closeness of fit" theory he espoused in 1965 and enlarged upon in 1993 provides a remarkably accurate insight into static aspects of damage recognition. Thirty years later, the general accuracy of this concept was confirmed by X-ray crystallographic studies of DNA repair proteins bound to site-specifically modified duplex DNA. The superb teaching and research environment created by Phil at Stanford was a major factor in my joining the DNA repair research community. As such, it is a privilege for Dmitry Zharkov and me to contribute to this special issue by providing some new insights into the dynamic aspects of DNA damage recognition Arthur P. Grollman.

1. Introduction

Imagine the Trans-Siberian railroad, 5867 miles long, obstructed by snowdrifts, struck by lightning, scorched by forest fires, and attacked by ferocious beasts and ravaging gangs, so that, on the average, one breakdown with potentially fatal consequences occurs each day in every 100 yards of track. Far from being a script for a blockbuster disaster movie, this scenario is what humans are exposed to daily, with the activity being multiplied by $\sim 10^{13}$, the approximate number of nucleated cells in our bodies. The railroad in this metaphor is DNA and it has been estimated that daily each cell receives $\sim 10^5$ insults to its primary structure [1,2], the majority resulting in base lesions. So, just as a railroad employs a cadre of trackwalkers to regularly inspect the rails, ties, embankment and other parts of the track, the cell maintains enzymes that survey the genome and correct damage inflicted by endogenous and exogenous agents.

Small nonbulky lesions constitute the majority of base lesions and are caused by unavoidable chemical processes, such as base deamination and oxidation [1,3] and by other chemical reactions that take place spontaneously in the living cell. These lesions primarily are repaired through the base excision repair (BER) pathway [2,4]. DNA glycosylases recognize and excise damaged bases, whereupon AP endonucleases hydrolyze the nascent abasic (AP) site. DNA integrity is restored with the participation of DNA polymerases, DNA ligases, and various accessory proteins. DNA glycosylases attract special attention, since they initiate repair of most BER substrates (except AP sites) and are the only BER constituents that exist as a family of enzymes with the same essential function but with different substrate specificities.