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Review

Transcription past DNA adducts derived from polycyclic aromatic hydrocarbons

David A. Scicchitano *

Department of Biology, 1009 Silver Center, 100 Washington Square East, New York University, New York, NY 10003, USA

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Abstract

The ability of a DNA lesion to block transcription is a function of many variables: (1) the ability of the RNA polymerase active site to accommodate the damaged base; (2) the size and shape of the adduct, which includes the specific modified base; (3) the stereochemistry of the adduct; (4) the base incorporated into the growing transcript; (5) and the local DNA sequence. Each of these parameters, either alone or in combination, can influence how a particular lesion in the genome will affect transcription elongation, resulting in potential clearance of the lesion via transcription-coupled DNA repair or in the formation of truncated or full-length transcripts that might encode defective proteins.

Keywords: DNA repair; DNA adducts; Transcription elongation

Contents

* Tel.: +1 212 998 8229; fax: +1 212 995 4015.
E-mail address: das2@nyu.edu.

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Prologue

It was quite exciting to be a member of Phil Hanawalt's laboratory in the 1980s. I still remember the moment when Isabel Mellon reported the news from his lab that the transcribed strand of an active gene was cleared of thymine dimers at a much faster rate than its nontranscribed counterpart. The resulting manuscript by Isabel Mellon, Graciela Spivak, and Philip Hanawalt, which was published in *Cell* [20], ushered in a new era, an era in which the fields of DNA repair and transcription would merge in ways that now seem logical but at the time were not even dreamed of. But dreams give rise to contemplation, and Phil's tremendously contemplative insights and his willingness to share them still inspire many of us to travel in new scientific directions, and perhaps that is the greatest contribution he could make to any of our careers—that, and providing an extended family of close colleagues like Allen Smith and Ann Ganesan.

1. Introduction

DNA adducts that are located on the template strand of active genes can impede the progress of elongating RNA polymerase (RNAP) complexes, an event that can have deleterious effects on transcription. Cells cannot tolerate stalled transcription complexes and have evolved various means to release them when they occur. In fact, the clearance of RNAP-blocking damage from the transcribed strand of actively expressed genes may well be facilitated by stalled RNA polymerases via a process called transcription-coupled DNA repair (TCR). The importance of TCR is observed in patients with the debilitating developmental disease called Cockayne's syndrome (CS) in whom the process of TCR is abnormal and transcription elongation may well be defective [1–4].

Studies using site-specifically damaged DNA templates have demonstrated that a wide range of DNA lesions can block the progress of elongating transcription complexes, but little is known about the particular features of DNA adducts that cause them to interfere with RNA synthesis. This article focuses on these issues, emphasizing DNA adducts derived from covalent attachment of polycyclic aromatic hydrocarbon (PAH) moieties to specific bases in DNA.

2. Transcription-coupled DNA repair

In cells, a collection of pathways maintains genomic integrity by repairing damaged DNA [1]. While numerous pathways exist, the most relevant to the clearance of PAH damage and to TCR is nucleotide excision repair (NER) [1,5]. Over 30 proteins are required to bring about NER in cells. Among them are seven proteins, XP-A through XP-G, that are named for the complementation groups associated with the disease xeroderma pigmentosum (XP) [6]. The XP proteins are required for DNA damage recognition and incision during NER. In eukaryotes, homologues of the human protein heterodimer XPC/HR23B bind to damaged DNA, marking it for excision [7–9]. This permits interaction of other XP homologues and additional NER-associated factors that remove a DNA oligomer that contains the damage [10–16]. A DNA polymerase then fills in the resulting gap, and ligase seals the DNA [17].

In many ways, TCR is a sub-pathway of NER. During TCR, the transcribed strand of active genes is cleared of damage faster than its complementary, nontranscribed strand or the genome overall [18–21]. TCR's principal distinguishing characteristic appears to lie in its reliance on using stalled transcription complexes as a recognition signal for DNA damage rather than the XPC/HR23B heterodimer. The stalled RNA polymerase complex probably recruits additional XP proteins and NER factors to remove the damaged DNA [20,22,23]. In addition, TCR requires CSA and CSB proteins whose genes are mutated in the CSA and CSB complementation groups of CS [22–24].

DNA adducts that are subject to TCR probably act as impediments to transcription elongation [4,25,26]. It is also likely that the stalled RNA polymerase must be removed from the lesion prior to repair—a process that is probably compromised in CS [22,23,27,28]. Elongation factors like SII might help the stalled polymerase reverse translocate, thus unmasking the lesion and making it accessible to repair proteins [29,30]. There is also evidence that RNA polymerase ubiquitination is involved in its removal from sites of blockage [31,32].

3. PAH-DNA adducts

PAHs are ubiquitous byproducts of incomplete combustion, and they include benzo[*a*]pyrene (B[*a*]P)