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Review

DNA repair during *in utero* development: A review of the current state of knowledge, research needs, and potential application in risk assessment

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ABSTRACT

Exposure to genotoxic chemicals during *in utero* development may lead to outcomes such as altered gene transcription, mutations, or cell death. Ultimately, such exposures may result in cancer, malformations, or functional deficits. As a mechanism that can limit the impact of genotoxicants in adults, DNA repair may also be an important factor that determines the outcome of the conceptus. This review of the literature examines the current understanding of DNA repair during *in utero* mammalian development by investigating the importance of maintaining genomic integrity and factors affecting susceptibility, including DNA repair. Most data have been derived from studies in rodent models focusing on DNA repair gene expression, which can vary according to developmental stages, tissues, and DNA repair pathways. Gene expression information is limited for humans but is suggestive that the major repair pathways exist during *in utero* development. Due to the complexities of DNA repair and its regulation by other pathways, available gene expression data may be limited for clarifying the role of DNA repair as a mechanism controlling the response to *in utero* exposures to genotoxicants. While not a comprehensive dataset, functional studies assessing *in utero* DNA repair capacity do demonstrate the variable ability of fetal tissue to remove DNA damage. Data gaps are recognized and recommendations for additional research using stems cells and traditional embryo models are identified. Finally, a brief discussion focuses on how data regarding *in utero* DNA repair may ultimately be utilized in health risk assessments of genotoxic chemicals.

Contents

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1. Introduction

Human and animal data demonstrate that stages of development can be critical windows of susceptibility to chemical exposures. Early life exposures to environmental pollutants can have immediate (e.g., in childhood) and latent health outcomes (e.g., in adulthood) (reviewed in [1]). A current area of interest in understanding the risk from prenatal stressors is the relationship between epigenetic changes and adverse health outcomes (reviewed in [2]). However, considerable research has also focused on the impact of direct and indirect genotoxicity and mutagenicity from *in utero* exposures. Herein we define genotoxic chemicals as those capable of damaging DNA, whereas mutagenic chemicals are capable of inducing permanent and inheritable changes to DNA. As reviewed by Anderson et al. [3], *in utero* exposures to various genotoxicants can lead to cancer in experimental animals. Additionally, these authors point out that developing animals can also have a higher sensitivity to tumor formation than adults. Outcomes other than mutations and cancer can also result from genotoxicity during in *utero* development.

In humans, transplacental exposure to environmental carcinogens can result in the formation of DNA damage and the induction of somatic mutations in newborns [4,5]. Baldwin and Preston-Martin [6] and Spector et al. [7] have highlighted the fact that *in utero* exposures to a number of agents including N-nitroso compounds, some pesticides, tobacco smoke, and dietary flavonoids are implicated as risk factors for health effects later in life. Irradiation provides an example of a genotoxic agent unequivocally shown to cause cancer in humans after *in utero* exposures, as concluded from a review of epidemiological data [8]. In addition to their carcinogenic potential from *in utero* exposures, the potential for teratogenesis and the induction of functional (e.g., neurological) deficits by genotoxic chemicals has been emphasized by Bishop et al. [9] and Wells et al. [10].

With the possibility of transplacental exposures to environmental genotoxicants, data about *in utero* DNA repair may inform human health risk assessments about potential health outcomes. Therefore, we posited that DNA repair during *in utero* development may be informative of how genotoxicants contribute to immediate and late onset health outcomes. This review briefly describes the biology of DNA repair and its significance during development, focuses on research that has addressed *in utero* DNA repair, attempts to identify research gaps and approaches for future research, and finally discusses the application of such data to health risk assessment.

2. DNA repair and development

While DNA damage can occur to germ cells [11,12], DNA repair during the period of preconception is not covered here but has been reviewed elsewhere [13,14]. Various physiological and biochemical processes may explain an enhanced sensitivity toward genotoxic chemicals during periods of development. While a number of reviews have discussed the toxicokinetic differences between juvenile and adult animals [15–17], additional factors may contribute to susceptibility from *in utero* exposures to potential carcinogens and genotoxicants (Table 1) [3]. The importance of factors including rapid cell proliferation on DNA metabolism, DNA repair, the production of endogenous reactive oxygen species, and the potential outcomes of *in utero* exposures to genotoxicants will be discussed below. With enhanced cell proliferation, genotoxicants have greater access to DNA strands undergoing transcription [18] or replication [19], which may result in transcriptional mutagenesis or tumor initiation [20]. The rapid cell proliferation and concomitant increase in DNA replication necessary for tissue development decreases the length of the cell cycle compared to adults, as demonstrated in rats [21]. A shorter cell cycle increases the chance that DNA lesions will escape repair mechanisms thereby increasing the likelihood for mutation fixation and cancer initiation. As discussed by Ginsberg [22], rapid cell proliferation during *in utero* development may also serve as a promotional mechanism allowing for the clonal expansion of initiated cells and tumor formation. As described later, the presence of DNA damage can interfere with proteins (e.g. transcription factors and histones) associated with DNA metabolism. Finally, the presence of overwhelming DNA damage during enhanced embryonic cell proliferation may drive cells toward apoptosis, ultimately reducing the number of cells within the developing conceptus [23].

Table 1
Factors that may determine *in utero* susceptibility to genotoxicants.

Process/phenomena
Number of target cells at risk
Sensitivity to cell killing
Effects of rate of cell division on fixation of mutation before repair can occur
Production of endogenous sources of reactive oxygen species
Ability to repair DNA damage
Effects of altered gene transcription
Expansion of clones of mutated cells as part of normal ontogeny
Presence of undifferentiated stem cells
Development of differentiated characteristics, including the ability to carry out metabolic activation of chemicals
Metabolic detoxification by placenta and/or maternal tissues
Metabolic detoxification by the conceptus
Immaturity of the endocrine and immunological systems

(Adapted from [3]).

2.1. DNA damage and repair

Of the processes listed in Table 1 that may increase *in utero* susceptibility toward genotoxicants, DNA repair may be an important determinant of how genotoxicants contribute to immediate and long-term health effects. Cells respond to a variety of DNA lesions, which arise from endogenous (e.g., cellular respiration, inflammation) and exogenous exposure to genotoxicants, using a number of DNA repair pathways and damage sensing mechanisms [24]. Boysen et al. [25] discussed covalent modifications to DNA bases that can result in the formation of DNA adducts, which can range in size from small, non-bulky lesions (e.g., N7-methylguanine) to large, helix-distorting adducts (e.g., N7-aflatoxin-guanine adducts). Additionally, DNA bases can undergo spontaneous depurination/depyrimidination [26] or become oxidized (for review see [27]). A further discussion of DNA oxidation by Pogozelski and Tulius [28] summarized how free radicals can cleave the DNA backbone leading to the formation of single and double strand breaks (DSBs). Depending on the chemical exposure (e.g., cisplatin, formaldehyde), cross-links can occur between DNA strands [29] or between DNA and proteins [30,31]. Additionally, as discussed by Ferguson and Denny [32], some chemicals intercalate themselves between DNA bases thereby causing structural changes to DNA.

Each repair pathway generally amends specific DNA lesions through a specific complement of repair genes (Table 2), of which upwards of 230 have been identified in humans and compiled elsewhere [33,34]. DNA repair pathways can be classified into excision repair (e.g., base excision repair [BER] and nucleotide excision repair [NER]), direct reversal (DR), mismatch repair (MMR), and double strand break repair (DSBR) pathways (e.g., homologous recombination [HR] and non-homologous end-joining [NHEJ]) (for reviews see [35–39]). The BER pathway removes small, non-bulky DNA adducts, abasics sites, and DNA single-strand breaks (SSBs). In general, BER excises a small stretch