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Mini-review

# An epitome of DNA repair related genes and mechanisms in thyroid carcinoma

Elisavet Gatzidou [a], Christina Michailidi [a], Sophia Tseleni-Balafouta [b], Stamatios Theocharis [a,*]

[a] Department of Forensic Medicine and Toxicology, National and Kapodistrian University of Athens, Medical School, Athens, Greece
[b] Department of Pathology, National and Kapodistrian University of Athens, Medical School, Athens, Greece

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ABSTRACT

Thyroid cancer presents a growing tendency during the last decades, particularly in regions affected by radiation exposure. The present review describes expression alterations and gene polymorphisms of DNA repair related molecules, leading to genomic instability and cell death, being associated with thyroid cancer. The referred variations in DNA repair related genes depict that indirect repair mechanisms are mainly correlated with thyroid gland carcinogenesis. Such abnormalities could participate in thyroid tumor development and progression and could be targeted for future prevention and therapy.



## 1. Introduction

Thyroid cancer is the most frequent endocrine malignancy with reported rapidly increasing incidence in recent years [1–3]. It consists of four forms: papillary, follicular, medullary and anaplastic, based on distinct histopathological criteria. The most common type is papillary thyroid carcinoma (PTC), which accounts for more than 80% of all thyroid malignancies [4]. PTC along with follicular and Hürthle cell carcinoma (a subtype of follicular thyroid carcinoma), is termed differentiated thyroid carcinoma (DTC), accounting for approximately 90% of all thyroid malignancies. Medullary and anaplastic thyroid carcinomas are less oftenly recognized [4].

The exact etiology of DTC remains still unknown, while exposure to ionizing radiation has been reported as a risk factor. Sources of ionizing radiation presume certain medical treatments as well as radiation fallout from power plant accidents or nuclear weapons. Potential predisposing genetic factors influence an individual's sensitivity to radiation and his/her susceptibility to DTC [5].

Ionizing radiation such as X- and gamma-rays cause a variety of DNA damage, including single- and double-strand breaks, leading to chromosome breakage and nucleotide alterations due to generation of free radicals [6]. This type of damage which relatively causes minor changes in the helical DNA structure is efficiently wiped out/amended by one of the most well conserved DNA repair systems that normally protect genetic integrity in cell populations. Impairment of DNA repair systems could predispose cells to genetic instability that is considered as a hallmark of cancer.

The present review article targets to detail the imperfections of components involved in DNA repair systems being related with a risk of developing thyroid carcinoma. Primarily, a general reference on mechanisms importing DNA damages and DNA repair systems is given, emphasizing on indirect ones, followed by alterations in genes of DNA repair systems being related with thyroid carcinoma formation.

## 2. Mechanisms importing DNA damages

### 2.1. Damages in the DNA replication system

Due to the great speed of the DNA synthesis, DNA polymerases may outstrip some bases in the maternal strand

* Corresponding author.
*E-mail address:* theocharis@ath.forthnet.gr (S. Theocharis).

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leaving behind unpaired bases, an apparatus loading damages known as DNA replication slippage [7].

The second and most common mechanism inserting damages covers the accession of a false base (mismatch) and consists the substrate for the mismatch repair mechanism which is reported below.

### 2.2. 2. Damages due to environmental and other factors

Most of the DNA damages are caused by environmental factors like radiation (ionizing, UV) and chemical carcinogens divided into direct, pro- and co-carcinogen factors (e.g. alkylating agents, aflatoxine B and TPA, respectively). However spontaneous changes are also quite possible to be induced [7]. Modification of sporadic DNA bases mainly covers deamination; with deamination of 5-methyl-cytosine where cytosine is converted to thymine, being very important. Methylated cytosines consist hot spot places for placement of punctual transmutation and depurination where once the damage is not corrected, adenine takes the place of the purine [7].

## 3. Prelude to DNA repair systems

The survival of a cell depends on the felicitous replication of its DNA. In multicellular organisms what matters is not only a fulfilled DNA replication but also the inerrable reproduction of the genetic material from one cell generation to the other. This is certified by DNA repair systems that repair damages caused by the replication system or by environmental or other factors as mentioned above. Fig. 1 extensively summarizes the main DNA repair systems and pathways with emphasis in genes included in thyroid carcinogenesis.

### 3.1. Direct repair mechanisms

#### 3.1.1. Repair during replication

As it is commonly known DNA polymerase III has the ability to choose the complementary nucleotide while producing the new strand and also distinguishes possible mistakes and refines the mismatched nucleotide acting with $3' \rightarrow 5'$ exonuclease effectiveness [8,9]. This proofreading ability incorporates and DNA polymerase $\delta/\varepsilon$ (pol$\delta/\varepsilon$).

#### 3.1.2. O6-MGMT repair

Methylguanine-DNA methyltransferase is a direct repair enzyme that interferes in the repair of damages in O6 position of guanine caused by endogenous and environmental alkylating agents, by removing the alkyl groups. The enzyme acts with a self-destruction mechanism [8,9].

### 3.2. Indirect repair mechanisms

#### 3.2.1. Excision repair systems

Excision repair system represents a form of DNA repair mechanisms found in various cell types. It involves recognition and removal of the damaged segment of the polynucleotide strand by a nuclease followed by resynthesis of

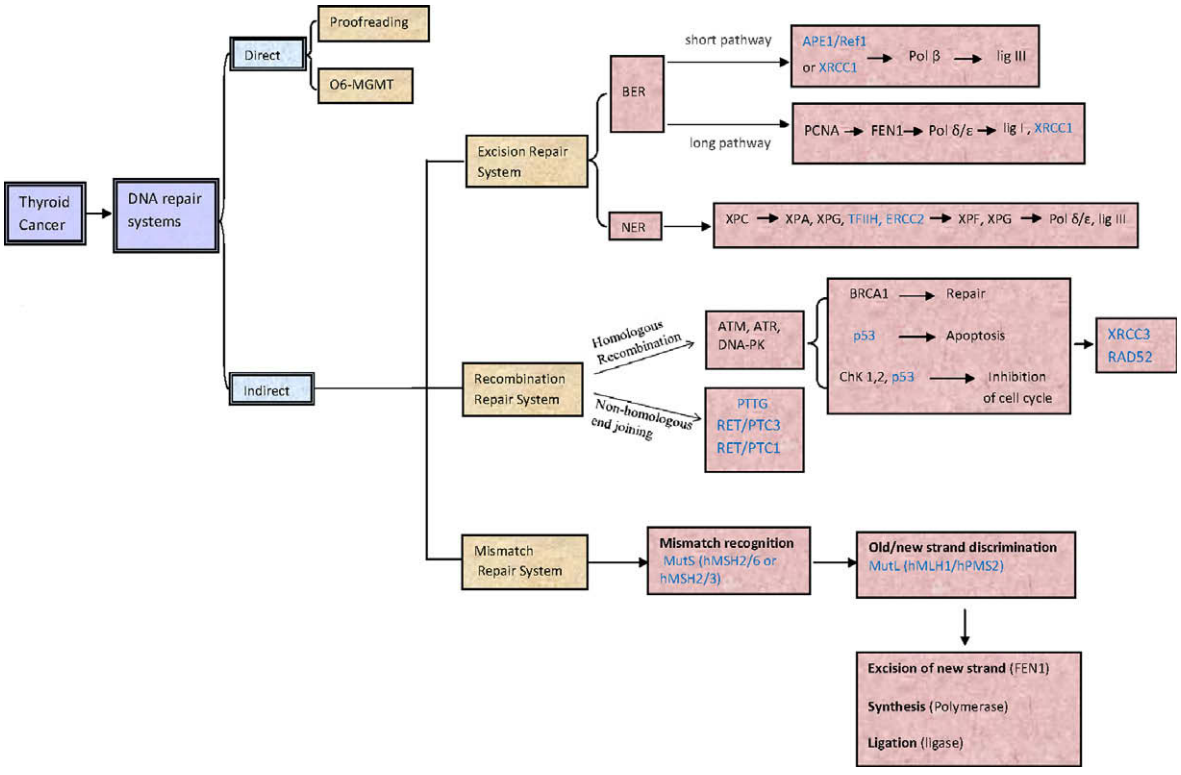


**Fig. 1.** DNA repair mechanisms and association with thyroid cancer (related genes are indicated with blue colour). (For interpretation of references to colours in this figure legend, the reader is referred to the web version of this paper.).