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Review Article

Redox regulation of genome stability by effects on gene expression, epigenetic pathways and DNA damage/repair

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ABSTRACT

Reactive oxygen and nitrogen species (e.g. H_2O_2, nitric oxide) confer redox regulation of essential cellular signaling pathways such as cell differentiation, proliferation, migration and apoptosis. In addition, classical regulation of gene expression or activity, including gene transcription to RNA followed by translation to the protein level, by transcription factors (e.g. NF-κB, HIF-1α) and mRNA binding proteins (e.g. GAPDH, HuR) is subject to redox regulation. This review will give an update of recent discoveries in this field, and specifically highlight the impact of reactive oxygen and nitrogen species on DNA repair systems that contribute to genomic stability. Emphasis will be placed on the emerging role of redox mechanisms regulating epigenetic pathways (e.g. miRNA, DNA methylation and histone modifications). By providing clinical correlations we discuss how oxidative stress can impact on gene regulation/activity and vise versa, how epigenetic processes, other gene regulatory mechanisms and DNA repair can influence the cellular redox state and contribute or prevent development or progression of disease.

Contents

Abbreviations: 5-hmC, 5-hydroxymethylcytosine; 5-mC, 5-methylcytosine; AP-1, activator protein 1; Ape-1, apurinic/apyrimidinic endonuclease 1; AREs, AU-rich elements; BER, base excision repair; COPD, chronic obstructive pulmonary disorder; DNMT, DNA methyltransferase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GPx-1, glutathione peroxidase-1; Grx, glutaredoxin; HAT, histone acetyltransferase; HDAC, histone deacetylase; HIF-1α, hypoxia inducible factor-1α; HO-1, heme oxygenase-1; HuR, mRNA-binding protein in the 3′-untranslated region; JmjC, Jumonji C domain-containing histone demethylases; Keap1, kelch-like ECH-associated protein 1; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; NER, nucleotide excision repair; Nox, member of the NADPH oxidase family; Nrf2, nuclear factor erythroid related factor 2; OxyR, transcription factor (hydrogen peroxide-inducible genes activator); PETN, pentaerithrityl tetranitrate; PHD, prolylhydroxylase; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; Trx, thioredoxin

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Introduction

The ability of every living organism to leave a progeny is encoded by its genome, which is a long DNA chain that contains all information about the particular organism. Genomes of living organisms can contain as few as 500 genes (e.g. mycoplasma) and as many as 20,000–25,000 for humans. Considering how valuable the integrity of a DNA molecule is, cells developed several protection systems. First, DNA is contained inside the nucleus, which is surrounded by a selectively permeable membrane. Secondly, DNA is also localized to the mitochondria, which can either be considered as a preservation strategy for the cell or a compartmentalization approach enabling better functional division between DNA molecules.

DNA located in the nucleus predominantly encodes for RNA molecules that later on can be translated to proteins. This means that every piece of information concerning a particular organism is encoded by nuclear DNA, starting from cell division parameters and finishing with information regarding programmed cell death. Information from DNA is processed via transcription mechanisms, leading to formation of another nucleic acid chain, namely RNA. Depending on the type of RNA molecule, translation to amino acid sequences, the building blocks for proteins, or other functional roles may occur. DNA located in mitochondria encodes all information necessary for its robust activity. In particular, mtDNA is responsible for storing, maintaining and successful implementation of information regarding among others, main components of mitochondrial electron transport chain (ETC) including cytochrome b, NADH dehydrogenase subunits, cytochrome oxidase subunits. In addition to direct transcriptional effects mediated by transcription factor binding to DNA epigenetic marks due to chemical modification of cytosine residues of DNA (DNA methylation) and histone proteins associated with DNA (histone modifications) can modulate gene activity and expression as well as chromatin.

Even though cells developed strategies to preserve the integrity of DNA, multiple factors can alter the structure of DNA [1], among which are UV irradiation [2], reactive oxygen and nitrogen species [3], or extrinsic chemical compounds [4]. On average, the DNA of a mammalian cell receives the following assaults per day: 200 cytosine deaminations, 3000 guanine methylations, 10,000 spontaneous depurinations, 10,000–100,000 oxidative lesions, 10,000 single-strand breaks, and 10–50 double-strand breaks [3,5–7]. Every type of DNA damage is source specific. For example, UV light is mostly known for strand breaks and/or DNA–DNA cross-links, as well as DNA–protein cross-link formation [8]. Reactive oxygen and nitrogen species predominantly induce specific base modification, such as 8-oxo-dG, 8-nitro-dG [9], or GC to TA transversions due to their high reactivity with strong nucleophilic sites on nucleobases [10]. External chemical compounds can introduce particular chemical groups, for example alkylation of DNA by methylnitrosourea [11] or N-methyl-N′-nitro-N-nitrosoguanidine [12] can cause DNA cross-links (e.g. mitomycin C, cisplatin) [13,14], or enhance formation of single- and double-strand breaks by sealing DNA-topoisomerase complexes [15]. One feature of the mammalian genome is the fact that every type of DNA aberration has a unique damage response in form of detection and repair systems. In conclusion, not only regulation of gene expression by transcription factors and epigenetic pathways, but also DNA damage/repair largely contributes to genome stability.

This review will outline that redox signaling and oxidative stress will affect expression, transcription and translation of genomic information not only by classical and epigenetic regulation of gene expression, but also by inflicting direct DNA damage and regulation of the activity of DNA repair enzymes. In the first section, we provide an overview on the different pathways and enzymatic systems that contribute to genome stability and readout of genomic information. In the second section, we focus on the impact of redox biology and oxidative stress on these different pathways. In the third section, we correlate these findings to the clinical situation. In the fourth section, we summarize the impact of redox biology and oxidative stress on genome stability as well as transcription and translation of genomic information.

DNA repair

Depending on the type of DNA modification different repair mechanisms will be activated in order to remove such damage. Whenever a toxic modification on a specific nucleobase appears or leads to formation of abasic sites, base excision repair (BER) is activated to resolve this problem [16]. Key players of the BER are DNA glycosylases (uracil-DNA glycosylase (UNG) [17], 8-oxoguanine DNA glycosylase (OGG1) [18], *n*th endonuclease III-like 1 (NTHL1) [19] and nei endonuclease VIII-like 1, 2 or 3 (NEIL1/NEIL2/NEIL3) [20]), all of which recognize different base modifications; DNA endonucleases such as apurinic/apyrimidinic endonuclease 1 (APE1) [21]; DNA polymerases (Polβ) and DNA ligases (Lig1) [22]. Specificity of this repair pathway is achieved by activity of the glycosylases that scan DNA molecules by slightly pulling the nucleotide strain. If there is a distortion of the helix, caused by a lack of hydrogen bonding between damaged Watson–Crick base pairs, these enzymes will flip this nucleobase out, insert it into the catalytic pocket, consequently cleave the N-glycosidic bond between the damaged base and the 2′-deoxyribose, and generate an apurinic- or apyrimidinic-(AP) site. All, AP sites are then processed by apurinic/apyrimidinic endonuclease 1 (APE-1), leaving clean 3′ and 5′ ends that allow DNA polymerase β (Polβ) and DNA ligase I (Lig1) to insert and ligate the appropriate base [23].

Nucleotide excision repair (NER) on the other hand, is able to remove larger and more complex types of damage found on DNA, like intra-strand and DNA–protein cross-links, and bulky formations [24]. Xeroderma pigmentosum, complementation group C (XPC), xeroderma pigmentosum, complementation group G (XPG), RAD23 homolog B (RAD23B), excision repair cross-complementation group 6 (ERCC6) and others function as damage identification molecules [25]. If the distortion was recognized during the replication process, the stalling of the replication fork will serve as an identification signal [26]. Upon receiving first NER up-regulation signals, the complex consisting of XPA, XPG [27], ERCC1, ERCC4, ERCC3 and replication protein A (RPA) acts as an excinuclease making two incisions in the DNA strand on either sides of the lesion. In a next step polymerases are activated to insert the correct DNA segment in the missing section and ligases will finish the repair process by sealing the strand.

If distinct DNA modifications are not repaired on time by repair machineries, they might lead to the formation of mismatches after incorrectly performed transcription. Unfortunately, such unfavorable transcriptional outcome can happen even without DNA damage. Mismatch signals as well as small insertion and deletion