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REVIEW

DNA repair pathways and their roles in drug resistance for lung adenocarcinoma

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Abstract

Lung cancer is the leading cancer type of death rate. The lung adenocarcinoma subtype is responsible for almost half of the total lung cancer deaths. Despite the improvements in cancer treatment in recent years, lung adenocarcinoma patients' overall survival rate remains poor. Immunetherapy and chemotherapy are two of the most widely used options for the treatment of cancer. Although many cancer types initially respond to these treatments, the development of resistance is inevitable. The rapid development of drug resistance mainly characterizes lung adenocarcinoma. Despite being the subject of many studies in recent years, the resistance initiation and progression mechanism is still unclear. In this review, we have examined the role of the primary DNA repair pathways (non-homologous end joining (NHEJ) pathway, homologous-recombinant repair (HR) pathway, base excision repair (BER) pathway, and nucleotide excision repair (NER) pathway and transactivation mechanisms of tumor protein 53 (TP53) in drug resistance development. This review suggests that mentioned pathways have essential roles in developing the resistance against chemotherapy and immunotherapy in lung adenocarcinoma patients.

Keywords Lung · Cancer · Lung adenocarcinoma · Drug resistance · DNA repair · Oncology

Abbreviations

TP53	Tumor protein 53
NHEJ	Non-homologous end joining
HR	Homologous-recombinant repair
BER	Base excision repair
NER	Nucleotide excision repair
SCLC	Small cell lung cancer
NSCLC	Non-small cell lung cancer
RFA	Radiofrequency ablation
DSBs	DNA double-strand break
HR	Homologous recombination
ARF	Alternative reading frame
ERCC5	Complementation group 5
DDB2	Damage specific DNA binding protein 2
Polk	DNA polymerase κ
FANCC	Fanconi anemia, complementation group C
MSH2	MutS homolog 2
MGMT	O-6-methylguanine-DNA methyltransferase
XPC	Xeroderma pigmentosum
XLF	XRCC4-like factor
PNK	Polynucleotide kinase
DHJ	Double Holliday junction
SDSA	Synthesis-dependent strand annealing
TNKS1BP1	Tankyrase 1 binding protein
APE1	Aurinic/apyrimidinic endonuclease 1
DNA polβ	DNA polymerase β
XRCC1	X-ray repair cross-complementing protein 1
LIGIII	DNA ligase III
PARP1	ADP-ribose polymerase-1
PCNA	Proliferating cell nuclear antigen
FEN1	Flap-endonuclease
RNAPII	RNA polymerase II
ERCC1	Excision repair cross-complementation group 1
CSA	Cockayne syndrome A
CSB	Cockayne syndrome B
EGFR-TKIs	EGFR tyrosine kinase inhibitors
ICI	Immune checkpoint inhibitors

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Introduction

Lung cancer is one of the leading cancers in incidence, death, and survival rates mainly due to the diagnosis of the disease at advanced stages with 75% of patients being metastatic at diagnosis [1]. The disease has a substantial economic burden on health systems as well as a negative social impact on patients and their relatives. Lung cancer can be classified into two main clinical groups: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [2]. NSCLC accounts for 80–85% and SCLC for 15–20% of all lung cancer patients [3, 4]. NSCLC can be further divided into three histological subtypes, namely adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Lung adenocarcinoma is the most common and fatal subtype with being responsible for almost 50% of all lung cancer deaths [5, 6].

Although targeted therapies promise new hope, currently, there is no effective treatment as the 5-year overall survival rate is still around 17% [7]. Surgery, alone or with following adjuvant chemoradiotherapy, is the most effective therapeutic option; however, it applies to only a limited number of patients who have no metastasis. Since the majority of patients with lung cancer are metastatic at diagnosis, the primary therapeutic intervention provided through nonsurgical approaches such as chemotherapy, radiofrequency ablation (RFA), radiotherapy, targeted therapies, immunotherapy, or a combination of these depending on the stage of the disease and development of the resistance [8].

Neoadjuvant or adjuvant chemotherapy are administered pre- or post-operatively, respectively. However, single or combination chemotherapy is the first option for patients who are not at advanced operational stages. Chemotherapeutics classified according to their mechanism of action, and they include: (A) DNA-interactive alkylating antineoplastic agents, (B) RNA and DNA blocking anti-metabolite agents, (C) Antibiotics that inhibit enzymes associated with DNA replication and transcription, (D) Topoisomerase inhibitors, (E) Mitotic inhibitors, (F) Corticosteroids [9]. Platinum-based antineoplastic agents, cisplatin and carboplatin, are primary therapeutics in the treatment of lung adenocarcinoma cases and is usually given in combination with paclitaxel, albumin-bound paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine, and pemetrexed [10]. Generally, treatment starts with the combination of two chemotherapeutics, one of which is either cisplatin or its derivative carboplatin. Cisplatin and its combinations aim for the generation of double-strand breaks (DSBs) in tumor cells. DBS are the most lethal types of DNA damage and cellular checkpoint mechanisms repair these parts of the genome. If not repaired DBS lead cell death and eventually both process eliminate the problem. When the initial chemotherapy-based treatment is not effective, second-line treatment with a single chemotherapeutic such as docetaxel or pemetrexed, or with targeted therapy or immunotherapy drug is used [11].

Cisplatin and carboplatin are alkylating agents, which show their antineoplastic effects through several mechanisms including prevention of DNA synthesis via attachment of alkyl groups to DNA bases, DNA damage by forming cross-links, and the initiation of mispairing of the nucleotides leading to mutations [12]. Gemcitabine can inhibit DNA replication resulting in DNA DSBs and fork stalling, recovery from which can be achieved through homologous recombination (HR) systems [13]. Vinorelbine is another compound that can be used with cisplatin or carboplatin in a combined way and also induces DSBs [14]. Irinotecan takes part in the inhibition of topoisomerase-I that results in the prevention of the DNA re-ligation leading to DNA DSBs [15]. Similarly, etoposide and adriamycin inhibit the DNA topoisomerase II and create a similar effect as irinotecan [16, 17]. Finally, pemetrexed can be used in combination with cisplatin [18], and it suggested that this combined therapy can also result in DNA DSBs, which might be repaired via HR or NHEJ pathways [19].

Innate and/or acquired resistance to platinum-based agents and other agents mentioned above widely observed in patients with lung adenocarcinoma. These agents interrupt replication and transcription mechanisms of DNA in lung adenocarcinoma cells. To overcome the toxicity of these agents, lung cancer cells increased DNA repair capacity [20].

Immunotherapy has emerged as a promising approach to provide effective treatment of lung adenocarcinoma. In this context, monoclonal antibody-based immunotherapeutics (cetuximab, bevacizumab, nivolumab, pembrolizumab, etc.) are extensively used in patients with lung adenocarcinoma either as monotherapy or in combination with other chemotherapeutics, antibodies and immune checkpoint inhibitors (ICI). Similarly with conventional chemotherapeutics, resistance to immunotherapy is an important clinical problem in lung adenocarcinoma treatment. Also, DNA repair pathways are involved in development of resistance mechanisms of the immunotherapy [21].

Our understanding of the mechanisms involved in the development of drug resistance has increased rapidly in recent years; however, the complete picture is still unclear mainly due to the involvement of the many biological processes including DNA repair mechanism, drug inactivation, drug efflux, and apoptosis in the development of the drug resistance [22]. Although complete interactome of the DNA repair genes is not elucidated yet, DNA repair pathways are accepted as the primary targets to prevent resistance to

chemotherapy drugs [23, 24]. According to the type of DNA damage, cells can initiate different DNA repair mechanisms to preserve cellular function, and these mechanisms are also driving tumor cells to develop chemotherapeutic resistance [26]. As a result, this literature review focused on the critical pathways that take part in the DNA repair mechanism or have a transactivation function on these pathways. Besides, we will discuss the potential relationship between these systems and the development of the chemotherapy drug resistance in lung adenocarcinoma.

Tumor protein p53 pathway

TP53 is a tumor suppressor gene, which encodes a nuclear phosphoprotein composed of four domains. These domains are a transactivation domain located at N-terminal, a DNA binding domain (core domain), a tetramerization domain (located at C-terminal), and a C-terminal negative regulatory domain [25, 26]. TP53 protein can interact with a broad range of proteins, but more importantly, it can also interact with DNA and regulates the expression of thousands of genes [27]. As a result, the TP53 pathway has substantial control on cellular homoeostasis since it can regulate vital cellular processes including apoptosis, senescence, metabolic changes, autophagy, cell cycle arrest, and DNA repair. Activation and regulation of these processes depend on various cellular stress signals [28]. These signals activate TP53 protein via post-translational modifications such as phosphorylation, ubiquitination, and acetylation [29]. Under the normal cellular conditions, TP53 protein exists at low concentrations due to the negative regulation of MDM2 (an E3 ubiquitin ligase) [30]. MDM2 controls the activity and concentration of TP53 by controlling its stability and subcellular localization [28]. Tumor suppressor alternative reading frame (ARF), another regulator of TP53 protein, is one of the most frequently mutated proteins in various human cancer types, including lung adenocarcinoma. ARF activates and stabilizes TP53 by activating MDM2 in the nucleolus. Also, Siva1 protein is involved in ARF-MDM2-TP53 regulation. This protein is another E3 ubiquitin ligase that physically interacts with ARF and regulates its degradation [31].

Furthermore, it has been shown that ATR and ATM proteins also have a critical regulatory function on TP53 activities after DNA damage. These proteins interact with Chk1 and Chk2, respectively, to initiate the DNA repair mechanism by arresting the cell cycle [32–34]. Moreover, ATM protein interacts with c-Abl, which also takes part in the activation of Chk1 in accordance with ATM. As a result, along with these proteins, c-Abl might also be considered as one of the most important proteins that take part in the upstream of the p53 regulation mechanism [35].

Once a cellular stress signal (DNA damage, metabolic dysfunction, oncogene activity, replicative stress, and hypoxia) is transmitted to TP53 protein, it is stabilized and accumulated in the nucleus [36]. Subsequently, it interacts with DNA and dominantly acts as a transcription factor [37]. Based on the type of sensed stress signal and the cell, TP53 regulates the expression of different proteins. Consequently, the cellular response will be adjusted by the interplay between the signaling pathways, which are relational with the proteins whose expression levels are altered by TP53. For instance, the TP53 pathway can activate DNA-repair and cell-cycle arrest mechanisms for minor DNA damage and apoptosis or senescence mechanisms for more reliable stress signals [38]. During the activation phase, TP53 binds the DNA region as a tetramer in a sequence-specific manner [39]. TP53 is one of the most frequently mutated proteins (70%) in patients with lung adenocarcinoma. These mutations include missense mutations, nonsense mutations, insertions, deletions, and splice-site mutations [40]. Somatic missense mutations are the most common type (almost 80%) among *TP53* mutations [41–43]. The majority of these mutations are single-point mutations that occur in the early phases of lung cancer and are located at the core domain (DNA binding domain) which lead TP53 protein to lose some of its functions or gain new ones [44, 45]. P53 mutants can be classified as DNA-contact (R248Q, R273H and R282W) and structural mutants (R175H, Y220C, G245S, R249S). Numerous in vitro studies have reported that p53 mutants promote proliferation, invasion, angiogenesis, and migration of cancer cells. Mainly, these mutants confer resistance to chemotherapeutics, and hence understanding of the role of mutant p53 is critical to design drugs in the treatment of lung adenocarcinoma [46, 47]. Several clinical studies reported that *TP53* gene mutations are important prognostic biomarkers for lung adenocarcinoma patients to understand drug resistance mechanisms of immunotherapies [48, 49]. The association between *TP53* mutations and immunotherapy was investigated in immunotherapy-treated 350 metastatic or unresectable NSCLC patients by Zhao and co-workers. Truncating of *TP53* mutations is associated with poor immunotherapy in NSCLC patients with lower tumor mutation burden [48]. In another clinical study, *TP53* mutations were examined in nivolumab, pembrolizumab, atezolizumab, anti-PD(L)-1 + anti-CTLA4 and docetaxel treated *KRAS*-mutant lung adenocarcinoma patients. Clinical data indicated that specific somatic alterations of *KRAS*, *STK11/LKB1* and *TP53* genes modulate therapeutic efficiency of ICI in these patients [49]. It is also stated that the combination of chemotherapy and immune-therapy increases the survival rate of NSCLC patients. More specifically, it is reported that the combination of pembrolizumab and docetaxel significantly improved the overall response and the progression-free survival of advanced NSCLC patients [50]. As a result,

it can affect the transactivation function of TP53 in a broad range of cellular processes, which can result in the progression of cancer and resistance to anti-cancer therapy.

All of the cellular processes which are controlled by TP53 signaling pathway (apoptosis, DNA repair, cell cycle arrest, and metabolic changes) are essential in tumor suppression and anti-cancer therapy resistance [51]. Despite the complete mechanism involved in the regulation of these pathways by TP53 [38], many studies unraveled several essential targets of TP53 which are involved in the regulation of these complex cellular processes. Here, based on the focus of this review, we will discuss the transactivation function of TP53 signaling on the cell cycle and DNA repair mechanisms, and its contribution to the development of the resistance against chemotherapy drugs in patients with lung adenocarcinoma.

During the regulation of cell cycle and DNA repair processes, TP53 initially mediates transient G1 cell cycle arrest [52]. This break gives a chance for cells to detect and fix the DNA damage [53]. It is reported that the vital gene regulated by *TP53* and exerts control on G1 cell cycle arrest is cyclin-dependent kinase inhibitor 1A (also known as CDKN1a, or p21), which is also involved in senescence regulation [54, 55]. Also, it has been shown that, even if they are not as central as *CDKN1a*, several other genes such as *Btg2*, *Caveolin-1 (Cav1)*, protein tyrosine phosphatase receptor type-V gene (*Ptprv*), and the promyelocytic gene (*Pml*) are also among the targets of *TP53* contributing to G1 cell cycle arrest [56, 57]. Besides G1 cell cycle arrest, *TP53* also exerts control on the G2/M transition phase. At this checkpoint, mitotic cell division takes place and *TP53* is suggested to regulate this process by controlling the expression of Reprimo, DNA-damage-inducible gene 45a (*Gadd45a*) and 14-3-3 sigma protein [53, 58]. During the DNA repair, based on the type of DNA damage, TP53 can activate appropriate repair mechanisms such as BER, NER, HR, and NHEJ pathways [59, 60]. Transactivation of these mechanisms is controlled by a broad range of adaptors, which is directly targeted by TP53. *PolH* gene, excision repair cross-complementing rodent repair deficiency, complementation group 5 (*Ercc5*), damage specific DNA binding protein 2 (*Ddb2*), DNA polymerase κ (*Polk)*, Fanconi anaemia, complementation group C (*Fancc*), mutS homolog 2 (*Msh2*), Gadd45a, *O*-6-methylguanine-DNA methyltransferase (*Mgmt*), *RAD51*, and xeroderma pigmentosum (*Xpc*) are among these targets [60]. The detailed mechanism of the transactivation of the DNA repair pathways by these adapters remains to be discovered [61]. However, many studies have shown that TP53 pathway has a significant role in tumor chemoresistance because of its control on these DNA repair mechanisms (HR, NHEJ, BER and NER) and its ability in DNA damage surveillance [62, 63]. Several studies focused on lung cancer also support these findings and conclude that the TP53 pathway takes a central role in lung cancer chemoresistance [62, 63]. With the significantly high mutational level of TP53 protein in patients with lung adenocarcinoma, alongside with these findings, we can count the TP53 pathway as an essential contributor to the development of chemotherapy drug resistance in patients with lung adenocarcinoma. The mechanism behind the regulation of DNA repair pathways with TP53 and its relation to chemotherapy drug resistance in patients with lung adenocarcinoma will be discussed in the following sections.

Non-homologous end-joining (NHEJ) pathway

NHEJ pathway is involved in the DNA DSBs repair mechanism. This pathway can effectively function at all phases of the cell cycle and allow tumor cells rapidly to develop resistance to chemotherapy drugs [64, 65]. Even if the transactivation dependent and independent control of TP53 on this pathway represented by several studies, the mechanism behind this control remains nebulous [66].

The NHEJ pathway has five central components. These components are Ku (Ku70 (XRCC6)—Ku80 (XRCC5)) heterodimer, DNA-dependent protein kinase catalytic subunit (DNAPKcs), X-ray repair complementing defective repair in Chinese-hamster cells 4 (XRCC4), DNA ligase IV, and XRCC4-like factor, also called Cernunnos (XLF). This pathway starts with the activity of Ku heterodimer. These two polypeptides bind the damaged ends of the DNA together and create a scaffold for the activity of DNAPKcs. Subsequently, DNAPKcs binds to the damaged ends of DNA with Ku and form a complex known as DNA-PK (Fig. 1, I) [67, 68]. This complex ties the damaged ends of the DNA together. During this process, activated DNAPKcs phosphorylates itself along with the other proteins, which also contribute to the DSB repair mechanism or takes part in DNA damage signaling (Fig. 1, II) [69]. This phosphorylation alters the conformation of DNAPKcs. As a result, other DSB repair factors (such as nucleases, DNA polymerases) can join the repair process or take part in ligation (Fig. 1, III) [70]. At the ligation phase, XRCC4 creates a complex with DNA ligase IV and regulates its joining function by stabilizing it [71]. At the final stage, along with XRCC4/DNA ligase IV complex, XLF, polynucleotide kinase (PNK), and Artemis proteins also work at the damaged ends of the DNA to fill the gaps and restore the original form of the DNA [72]. In mammalian cells, an alternative pathway also exists, which does not require Ku and DNAPKcs proteins to function [73].

In several studies, it has been demonstrated that inhibition of this pathway significantly reduces the resistance against chemotherapy drugs. The studies acknowledge DNA-PKcs as the primary target to block the activity of the

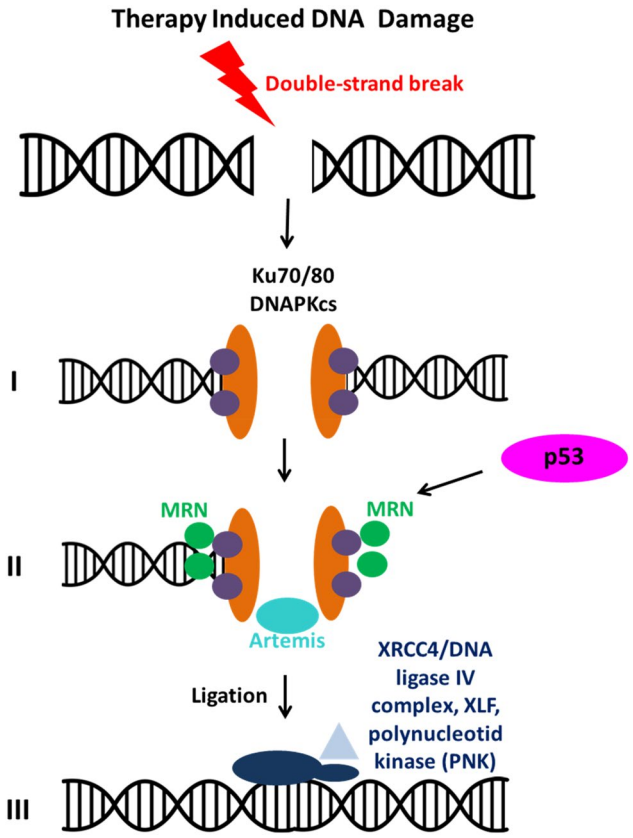

Fig. 1 Schematic representation of the NHEJ pathway. **I** Ku70/Ku80 heterodimer senses and binds the DSBs, stabilizes these damaged DNA ends and then recruits DNA-PKcs. **II** DNA-PK activates NHEJ pathway effector (such as ligase IV/XRC4, XLF, etc.) via phosphorylation. **III** Finally, broken ends of DNA aget re-ligated by activated effectors (adapted from Ref [74])

NHEJ pathway because of its central role. Along with these findings, many studies have reported the high expression levels of DNA-PKcs protein in NSCLC patients, including adenocarcinoma [75]. To sum up, the NHEJ pathway is one of the primary mechanisms that result in the development of the resistance against chemotherapeutic agents in lung adenocarcinoma.

Homologous recombination (HR) pathway

Another important pathway, which takes part in the DNA repair mechanism and has a critical role in the development of the drug resistance in lung adenocarcinoma, is the HR pathway. This critical pathway also takes part in the repair of DSBs along with NHEJ. NHEJ performs repairs based on the re-ligation of the damaged DNA ends without using the homologous DNA. On the other hand, the HR pathway can perform the error-free repair of DSBs based on the significant sequence homologies of intact DNA strands [76]. As this pathway exerts error-free repair based on the homologous strand of DNA, it is only active during the G2 and S stages of the cell cycle. Thus, sister chromatids, which are available at these stages, can be used by the HR pathway as a template [77]. Besides DSBs of DNA, DNA lesions, which occur at the replication forks because of the effect of the many anti-cancer drugs, are also among the substrates of this pathway [78]. For example, it is reported that the DNA damaging chemotherapy drugs such as cisplatin and PARP inhibitors are more active on the HR pathway defected tumors [79].

The activity of this pathway can be divided into three main steps: resection of damaged DNA ends (presynaptic), polymerization of homolog DNA (synapsis), and ligation (postsynaptic) [80]. The first phase starts with the generation of a key compound composed of Mre11, Rad50, and Nbs1 proteins. This compound is known as heterotrimeric MRN complex (Fig. 2, I). As the name suggests, this compound performs trimming of the damaged ends of DSBs from 5' to 3' end together with CtIP protein to form single-stranded DNA (short three overhanging ends) [81, 82]. This step continues with the combined function of BLM helicase (Bloom syndrome, RecQ helicase-like) and exonuclease 1 (Exo1) [83]. In the second phase, replication protein A (RPA) binds to the ends of the single-stranded DNA to take out the corruptive secondary structures and allow the binding of the Rad51 recombinase (Fig. 2, II). After the removal of the secondary elements, Rad51 replaces RPA with the help of several mediator proteins such as BRCA2, Rad52, and paralogs of Rad51. XRCC2, XRCC3, Rad51B, Rad51C, and Rad51D are among the paralogs of Rad51 [84]. Rad51 and its paralogs are essential proteins in the HR pathway as these proteins carry out the homology searching on sister chromatid [85]. Once the suitable homologous DNA found (template), these proteins start and regulate the invasion of the template by damaged DNA strand (Figure-2, III). This stage is also known as D-loop formation which is followed by the start of the synthesis from the damaged 3' end by DNA polymerase and subsequently, the ligation by DNA ligase I to form a four-way junction structure, known as DHJ (Fig. 2, IV) [86]. DHJ can be resolved in three different ways. These are, (i) symmetrical cleavage by GEN1/Yen1, (ii) asymmetrical cleavage by Mus81/Eme1 or (iii) BLM-Top III α complex [87–89]. The resolution step results in the error-free repair of the DSBs. An alternative to DHJ formation is the SDSA pathway, a part of HR (Fig. 2, V). The invading strand is displaced and annealed with the other end of damaged DNA following the DNA synthesis process in the SDSA pathway [83].

As explained previously, the Rad51 protein has a central role in the HR pathway. Previous studies represent that *TP53* regulates the expression of *Rad51* [90, 91]. In addition to its trans-activation dependent regulation, TP53 also directly

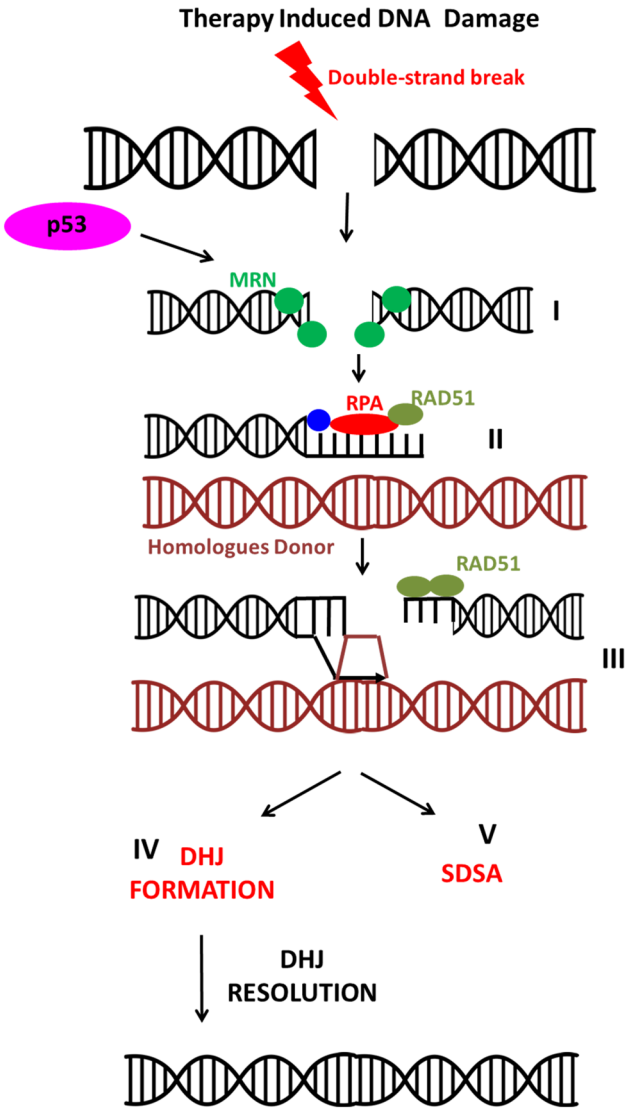

Fig. 2 Schematic representation of the HR pathway. **I** Trimming the damaged DNA ends by MRN complex. MRN is the crucial complex of the HR pathway, which is composed of Mre11, Rad50 and Nbs1 protein. **II** RPA binds to single-stranded ends of DNA to take out the disruptive secondary structures and lead RAD51 binding. Following this, Rad51 takes place in searching for suitable homologous DNA for the repair process. **III** Once the appropriate homologous DNA found (template), damaged DNA invades the template. This process is also known as D-loop formation. **IV** Finally, a four-way junction (also called double Holliday junction (DHJ)) forms and resolves. Resolution step results in the error-free repair of the damaged DNA. **V** Synthesis-dependent strand annealing (SDSA) is an alternative pathway to DHJ. The invading strand is displaced and annealed to the other end of damaged DNA during the invasion in the SDSA pathway (adapted from [74])

interacts with Rad51 and inhibits its activity, these regulatory functions of TP53 can represent the control that it exerts on the HR pathway [92].

The foci formation of this protein is regulated by tankyrase one binding protein one (TNKS1BP1) which also known as TAB 182. It has been demonstrated that the overexpression of this protein elongates the S phase of the cell cycle, which is also essential for the activity of the HR pathway. Also, it has been reported that TNKS1BP1 is highly expressed in lung adenocarcinoma patients and inhibition of the expression of this protein significantly reduces the Rad51 foci formation resulting in the inhibition of the HR pathway [93]. These findings suggest that, via the activation of TNKS1BP1, the HR pathway can be a responsible mechanism to develop rapid resistance to chemotherapy drugs in patients with lung adenocarcinoma.

Furthermore, AXL (a receptor tyrosine kinase) is associated with metastasis, invasion, and migration in many cancers along with NSCLC [94, 95]. Down-regulation or inhibition of AXL leads to a decrease in the expression of DNA repair genes and the foci formation of Rad51, which result in blocking the HR pathway [95]. Inhibition of AXL leads to accumulation of DNA damage through blocking homologous recombination. Combined treatment of an NSCLC cell line with AXL inhibitor (TP0903) and PARP inhibitor (olaparib) resulted in a significant decrease in the growth compared to single inhibitors alone; rendering AXL as a useful therapeutic target companion to reduce resistance to chemotherapy.

Base excision repair (BER) pathway

BER mechanism is another pathway related to the chemotherapy drug resistance in lung adenocarcinoma. This highly conserved pathway used to restore thousands (~30,000) of endogenous DNA damages that occur in each of the human cells daily. This pathway fixes small covalent modification, which does not cause DSBs. The targeted DNA damages by the BER pathway are including most of the oxidative damages, alkylation, depurination, and deamination, all essentials for the healthy growth and development of the mammalians. Dysfunction of this pathway results in severe diseases in humans, such as cancer and neurological disorders [96].

BER pathway performs its function in several phases [98]. The first step is the identification and extraction of the damaged bases of the DNA (Fig. 3, I, left-side). This process carried out by DNA glycosylases, and these glycosylases can be divided into four groups according to their substrates. These groups include methyl-purine glycosylase, uracil/thymine glycosylases, 8-Oxo-G repair glycosylases, and oxidized pyrimidine glycosylases [99]. It is known that *TP53* regulates the expression of *8-Oxo-G* repair glycosylases [100]. Most of the bases damaged by the chemotherapeutics can be counted among the substrates of these four glycosylases [96]. Once the damaged base has been removed, the removal site of the DNA (abasic site as a result of hydrolysis) needs to be cleaved and removed before the

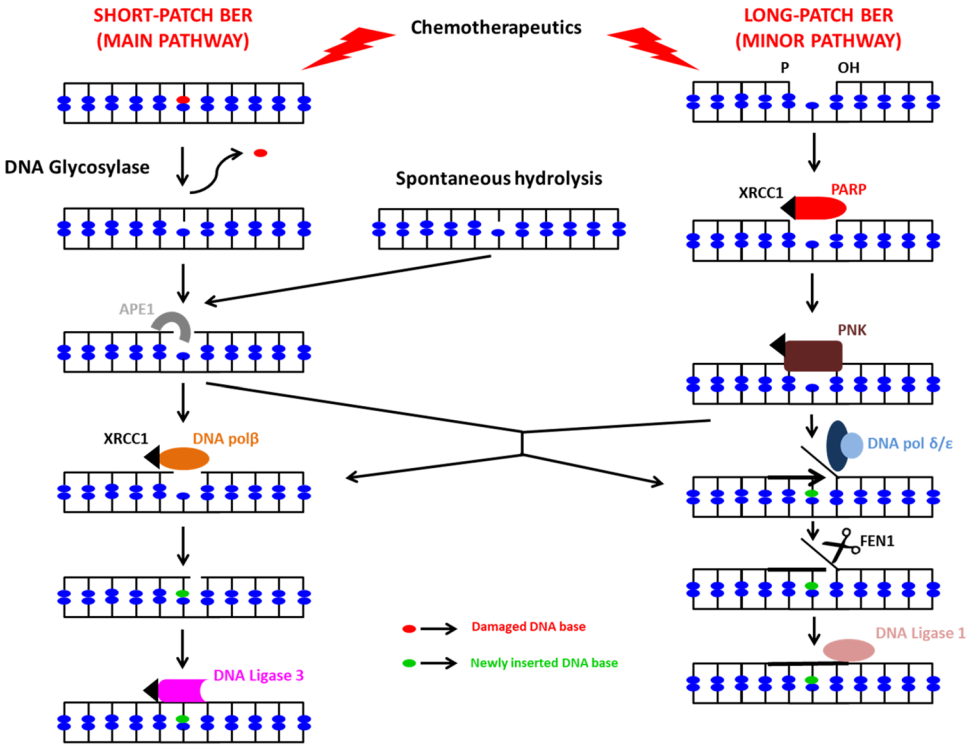

Fig. 3 Schematic representation of the BER pathway. Short-Patch: **I** Pathway starts with the identification and extraction of the damaged bases by DNA glycosylases. **II** APE1 cleaves and removes the abasic site. **III** After the removal of abasic site, XRCC1 and DNA polβ binds to the damaged region and inserts missing base (**IV**). **V** Following the insertion of missing base, DNA ligase 3 seals the DNA nicks. Long-Patch: I) XRCC1 and PARP1 detect and bind the damaged site of DNA and work as scaffolding proteins. **II** Followed by PCNA and DNA polδ/ε/β binding to damaged DNA site. They perform the DNA repair and displace the damaged strand. **III** Subsequently, FEN1 cuts the displaced damaged DNA strand. **IV** Finally, DNA ligase 1 seals the repaired site of DNA and long-patch gets completed (adapted from Ref. [97])

next step of the repair mechanism to prevent transcriptional problems [101].

For this reason, in the second phase of the pathway, apurinic/apyrimidinic endonuclease 1 (APE1) takes place to cleave and remove this a basic site (Fig. 3, II, left-side). DNA polymerase β (DNA polβ) then binds to the damaged region of DNA along with X-ray repair cross-complementing protein 1 (XRCC1) and inserts the missing base (Fig. 3, III and IV, left-side) [102–104]. Several studies suggested that at this stage TP53 can bind to DNA in association with APE1 to enhance its activity and it is also reported that the activity of the DNA polβ is also correlated with the amount of TP53 [66]. At the final stage, the BER pathway seals the DNA nicks, generated as a result of the repair process, by using the DNA ligase III (LIGIII) (Fig. 3, V) [105]. This mechanism is known as short patch repair, and it is the dominant mechanism of the BER pathway (Fig. 3, left-side).

An alternative minor mechanism of the BER pathway, also referred to as long patch repair mechanism is involved in the repair of the single-stranded DNA breaks (Fig. 3, right-side). Here the damaged DNA site is being bounded by two essential scaffolding proteins which are XRCC1 and poly ADP-ribose polymerase-1 (PARP1) (Fig. 3, I, right-side) [106]. In this mode, the DNA repair performed by proliferating cell nuclear antigen (PCNA), DNA polβ, DNA polδ, and DNA polε connect 2 to 15 nucleotides and displace the damaged strand (Fig. 3, II, right-side) [97]. Flap-endonuclease (FEN1) then takes place to split the displaced extension of DNA bases (Fig. 3, III, right-side), and finally DNA ligase one seals the repaired site of DNA (Fig. 3, IV, right-side) [107].

Many different cancer types can develop resistance to chemotherapeutics through this mechanism [108]. Many studies have shown that inhibition of BER pathway is significantly reducing the chemotherapy resistance in a wide range of cancer types, including lung cancer [109]. It has been demonstrated that XRCC1 protein (one of the significant scaffolding proteins in both alternative mechanisms of BER) has significantly high expression levels in patients with lung adenocarcinoma [110]. Besides, it has also been shown that there is a significant correlation between the overexpression of XRCC1 protein and chemotherapy drug resistance in NSCLC [111].

EGFR tyrosine kinase inhibitors (EGFR-TKIs) are also commonly used chemotherapeutics to treat advanced NSCLC adenocarcinoma patients [112]. One of the suggested mechanisms of the resistance against the epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) is the dysregulation of the PI3K/AKT/mTOR signaling pathway. Afatinib and sirolimus are two commonly used drugs for NSCLC treatment. These drugs are used in a combined manner to see the efficiency in reversing the gained EGFR-TKIs resistance by Dr. Rosell and colleagues. However, the results were not as successful as expected, which shows further clinical development of this combination required [113]. Erlotinib one of the most commonly used drug in the treatment of NSCLC patients demonstrated good efficacy according to the EURTAC trial especially for

patients who carries EGFR mutations. These mutations are specifically deletion in exon 19 and L858R variation in exon 21 [114]. A second-generation EGFR-TKIs inhibitor, dacomitinib, is also commonly used in the treatment of metastatic NSCLC patients. In literature, it is mentioned that, because of the toxicity of the drug, with tolerable dose modifications, this drug can improve the patients' survival [115]. EGFR-TKIs inhibit Hsp70 phosphorylation and stimulates ubiquitination of Hsp70 in lung adenocarcinoma cells which results in the degradation of this protein. Hsp70 is an essential promoter of the BER as it activates the APE1 and Pol β enzymes of this pathway. However, low-dose treatment of erlotinib also results in the emergence of EGFR T790M mutation on exon 20, which cause resistance against EGFR-TKIs in lung adenocarcinoma patients [116]. Therefore, inactivation of the BER pathway via Hsp70 degradation is a critical process in the formation of EGGR T790M mutation mediated erlotinib resistance in lung adenocarcinoma cells.

A recent study demonstrated that organophosphate pesticides (OPPs) constitute oxidative DNA damage in A549 lung adenocarcinoma cells. BER pathway promotes lung cancer cell survival and proliferation against OPP-induced oxidative stress [116]. Finally, outputs of these studies illustrate the importance of the BER pathway for lung adenocarcinoma tumors to develop resistance against chemotherapeutics.

Nucleotide excision repair (NER) pathway

NER pathway is one of the primary DNA repair mechanisms in mammalian cells targeting the extraction of massive DNA damage. These DNA lesions are composed of nitrogenous bases that are affected by ionizing irradiation, chemically active endogenous metabolites such as reactive oxygen, electrophilic chemical mutagens, UV light, and chemotherapeutic drugs [117]. This pathway functions through two different mechanisms based on the location of the damage. If the damage is on the side of the genome, which is not actively transcribed, the global genome NER (GG-NER) mechanism takes place to fix the DNA. Otherwise, transcription-coupled NER (TC-NER) gets activated [118].

NER pathway starts with the consecutive assembly of various proteins at targeted bulky DNA lesions. This pathway has similar cut, repair, and patch mechanisms with BER, but the derivation of the protein complexes, which take part in those steps, is much more complicated. In the case of GG-NER, surveillance and the binding of the identified damaged side of the DNA performed by XPC/hHR23 heterodimer (Fig. 4, I, left-side). This binding results in the local opening around the damaged bases of the DNA [117]. The multifunctional transcription factor TFIIH and XPG then interacts with the damaged region through this opening (Fig. 4, II). TFIIH has nine subunits, XPB and XPD helicase subunits bind to the damaged side of the DNA and loosen it in opposite directions by working together with RPA complex (the eukaryotic single-stranded DNA binding protein complex) and XPA protein (Fig. 4, III) [120]. In addition to this, TP53 directly interacts with the XPB and XPD subunits of TFIIH and modulates their helicase activities [121, 122]. Besides these contributions, TP53 also controls the expression of XPC, which is another vital protein for GG-NER pathway [123].

In the case of TC-NER, except XPC, all of the other proteins employed in GG-NER pathway are also used. The identification of the damaged DNA site in TC-NER mechanism starts with the stalling of RNA polymerase II (RNAPII) elongation on the damaged strand [124]. Along with RNAPII, Cockayne syndrome A (CSA) and B (CSB) proteins also predicted to take part in this phase and replace RNAPII to allow NER proteins entrance to the damaged lesion (Fig. 4, I, right-side) [125]. It thought that these proteins (CSA and CSB) are helping the assembly of TFIIH, XPG, XPA and RPA on the damaged side of DNA (Fig. 4, III). Following the recruitment of these three proteins and protein complexes, around 30 nucleotides long DNA stretch, which includes the damaged region of DNA, gets unwound. In the repair step, both mechanisms (GG-NER and TC-NER), first extract the oligonucleotide lesion composed of approximately 30 nucleotides and include the damaged side by using two structure-specific endonucleases, XPG and XPF/ERCC1 (Fig. 4, IV). From these two endonucleases, XPG cuts from the downstream (3') and XPF/ERCC1 cuts from the upstream (5′) of the DNA damage. It reported that the cuts made by XPG is about 5-6 nucleotides away from the lesion and the ones made by XPF/ERCC1 is about 20-22 nucleotides away [126]. After the oligonucleotide removal, DNA polymerase (Pol ε, Pol δ, or Pol κ) resynthesizes the resulting gap by using the undamaged strand of DNA as the Ref. [127]. Finally, the repaired part of the strand sealed by DNA ligase I, and the function of the NER pathway gets completed [118].

As mentioned above, excision repair cross-complementation group 1 (ERCC1) protein is one of the critical components of the NER pathway. This enzyme forms the critical NER complex, which takes part in the removal of damaged lesion of DNA and allows DNA polymerase to repair the DNA [128]. Having a regulative role in the creation of a suitable environment for the DNA polymerase makes ERCC1 an indispensable component of this pathway [128]. Many studies have reported that this protein is an essential indicator of chemotherapy resistance and inhibition of which results in a significant decrease in NSCLC chemotherapy resistance [129]. Especially, platinum-based drugs (such as cisplatin and carboplatin) are important anti-cancer agents for patients with NSCLC adenocarcinoma. These drugs serve anti-proliferative effects by inducing DNA damage in

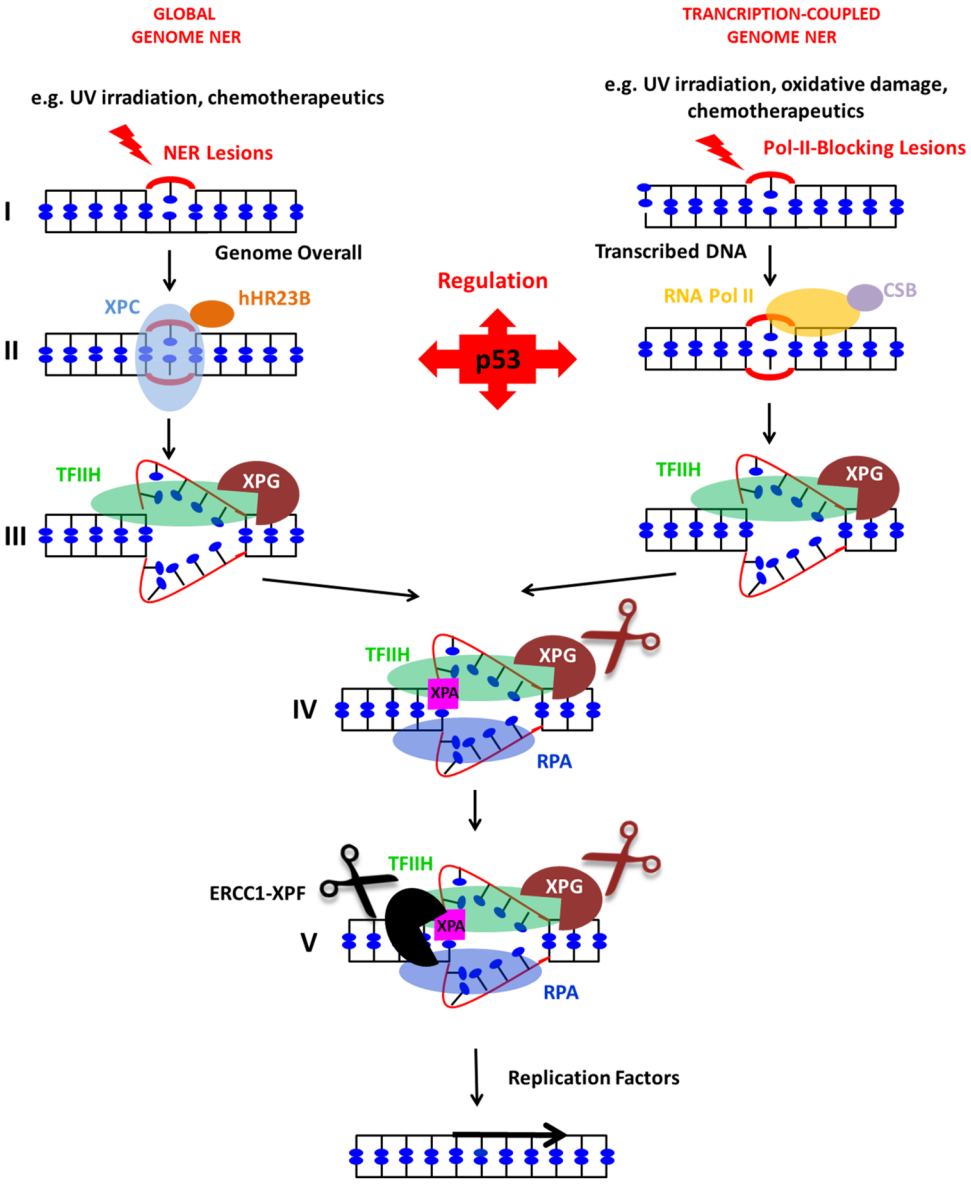

Fig. 4 Schematic representation of the NER pathway. **I** In GG-NER, XPC/hHR23 heterodimer detects and binds the damaged DNA site. In TC-NER, this RNA pol II, CSA and CSB undertake this duty. **II** Following detection of the damaged DNA region, in both mechanisms, TFIIH and XPG first bind to detected DNA site. **III** Subsequently, XPA and RPA also assembled with TFIIH and XPG on the damaged site. **IV** After the recruitment of these proteins and complexes, around 30 nucleotides long DNA strand which also includes damaged site gets unwound. Finally, endonucleases, XPG and XPF/ERCC1 cut the loose part of the strand. Then replication factors (DNA polymerase (Pol ε, Pol δ, or Pol κ) and DNA ligase I) resynthesizes the resulting gap and seal it (adapted from Ref. [119])

cancer cells. Many experimental and computational studies reported that, NER pathway and related genes involved in repair processes of platinum-based DNA damage [130]. Also, many other studies reported significantly high expression levels of ERCC1, specifically for lung adenocarcinoma patients [131]. Cetuximab is an anti-EGFR monoclonal antibody which is widely used in combination with conventional drugs, such as cisplatin and docetaxel, as first-line treatment with in patients with advanced NSCLC. Cetuximab inhibits proliferation, metastases and invasion of lung cancer cells, and stimulates apoptosis leading to high survival rates of patients with NSCLC [132]. Li and co-workers reported that overexpression of ERCC1 inhibited EGFR activation and stimulated resistance to cetuximab combined with cisplatin in lung adenocarcinoma cells [133]. Collectively, the NER pathway can also be listed among the other critical DNA repair mechanisms, which contribute to the development of the chemotherapy drug resistance in patients with lung adenocarcinoma.

Conclusion

Lung cancer is the deadliest cancer type, and lung adenocarcinoma is responsible for half of lung cancer deaths. Chemotherapy, an anti-cancer treatment exerting its effect through damaging DNA of the tumor cells, is one of the most commonly used strategies to fight against lung adenocarcinoma. However, drug resistance develops rapidly in those patients. DNA repair mechanisms are mainline of the defense against the drug resistance in patients with lung adenocarcinoma (Supplementary File). Although

many studies have performed to understand the mechanism behind the regulation of these pathways, the complete picture remains unclear. For example, even the mechanism of these pathways is mostly explained; there is still limited knowledge about cross-interactions between these pathways. However, a clear understanding of the crosstalk between these repair mechanisms is vital to understand the global system (DNA repair interactome) behind the development of chemotherapy drug resistance in patients with lung adenocarcinoma. Once DNA repair interactome is enlightened accurately, proteins that regulate the transactivation mechanisms can maintain the work of the individual DNA repair mechanisms in harmony. Furthermore, they can take part in the reprogramming of DNA repair interactome to compensate for the lost/decreased function when one of the pathways is inhibited. As a result, much more effective clinical applications can be developed to overcome this obstacle in the treatment of patients with lung adenocarcinoma.

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Declarations

Conflict of interest The authors confirm that this article content has no conflicts of interest.

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