Important Roles of ERCC1 in DNA Repair and Targeted Therapy

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1 Functions of ERCC1 in Multiple DNA Repair Pathways

The ERCC1 protein (excision repair cross-complementing rodent repair deficiency, complementation group 1) forms a heterodimer with the Xeroderma pigmentosum group F (XPF) endonuclease (also known as ERCC4), and the heterodimeric endonuclease catalyzes the 5′ incision in the process of excising the DNA lesion. The ERCC1–XPF heterodimer has an important role in genome maintenance. While most of the DNA repair proteins function only in a specific repair pathway, ERCC1–XPF is involved in multiple DNA repair pathways and telomere maintenance, making this heterodimer not only an attractive therapeutic target, but also a biomarker to predict treatment outcome.

The classical role of the ERCC1–XPF heterodimer lies in its involvement in the nucleotide excision repair (NER) pathway. NER has been extensively studied and the core mechanism is relatively well understood. It consists of three main steps: (1) lesion detection, (2) dual incision to remove an oligonucleotide containing the lesion, and (3) repair synthesis. ERCC1–XPF complex and the xeroderma pigmentosum group G (XPG) endonuclease are responsible for the dual incision step to release the lesion-containing oligonucleotide. XPG cuts 3′ to the damaged base, while ERCC1–XPF incises DNA 5′ to a lesion. Only XPF contains the nuclease domain of the ERCC1–XPF complex, but it requires ERCC1 for subsequent nuclease activity [1]. ERCC1 is essential for heterodimer positioning, as the central domain of ERCC1 binds with maximal affinity to single-stranded overhangs 15 nucleotides or longer with a preference for 5′ overhangs [2]. XPA appears to have a role in damage verification and is also necessary to load and position the ERCC1–XPF complex correctly onto the damaged DNA in order to start the incision process [3].

NER is one of the most versatile of all DNA repair mechanisms dealing with many different kinds of DNA damage that occur in the form of bulky adducts [4]. Typical substrates for NER include UV-induced photoadducts such as cyclobutane pyrimidine dimers (CPDs) and (6-4) photoproducts [5], intrastrand cross-links, and bulky chemical adducts. Of note, NER is an important pathway in the repair of intrastrand cross-links and bulky adducts that are induced by chemotherapy.

Unlike other NER factors, ERCC1–XPF heterodimer is also involved in multiple repair pathways, including double strand break repair (DSB) and interstrand cross-link repair (ICL). Homologous recombination (HR) is regarded as being an error-free process to repair DSB. A template, usually a sister chromatid, is needed to carry out the repair event [6]. It was proposed that ERCC1 was required for removal of long nonhomologous tails from 3′-OH ends of invading strands during targeted homologous recombination in Chinese hamster ovary cells [7].

For the repair of ICLs, taking the incision activities of the ERCC1–XPF heterodimer into account, it was proposed that a Y structure near the damage is first formed, for example, during DNA replication. ERCC1–XPF then cleaves at the 3′ side of one arm of the ICL and then makes an additional incision at the 5′ side. The replication fork collapses and recombination and NER events can take place to complete the ICL repair [8]. Fisher and coworkers found that the heterodimer does

not only cut 5′ of the psoralen lesion but also cuts 3′ of the ICL, resulting in a DSB near the cross-linked site. Therefore, ERCC1–XPF appears to be involved in unhooking of ICLs [9].

Furthermore, the ERCC1–XPF complex also plays roles in telomere maintenance where it interacts with the telomere binding protein 2 (TRF2). At telomeric ends, ERCC1–XPF appears to be required for degrading 3′ G-rich overhangs when TRF2 function is inhibited [10]. In addition, over-expression of TRF2 in mouse keratinocytes led to XPF-dependent telomere loss, increased DNA damage, premature ageing and cancer [11]. Considering the important roles of ERCC1 in multiple DNA repair pathways and telomere maintenance, it may serve as a potential therapeutic target to enhance treatment efficacy.

2 ERCC1 and Clinical Outcome of Lung Cancer

Lung cancer is the leading cause of cancer deaths in American men and women; there are estimated 221,130 new cases and 156,940 deaths in 2011 [12]. It can be classified into two subtypes, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The standard treatment for lung cancer includes platinum-based chemotherapy in combination with other non-platinum based regimens.

ERCC1 single nucleotide polymorphisms (SNPs), mRNA expression and protein expression levels have been associated with the sensitivity to chemotherapy with potential application as biomarkers for predicting treatment response and survival in lung cancer patients. We have summarized the results of several relatively larger studies evaluating the prognostic value of ERCC1-based biomarkers in lung cancer (Table 1). The two common *ERCC1* SNPs, *C354T* and *C8092A* were investigated in 115 NSCLC patients and the results showed a significant association between both SNPs and response to platinum based chemotherapy [13]. In 158 never-smokers with adenocarcinoma, *ERCC1 8092AA* genotype was associated with better response to gemcitabine/cisplatin [14].

ERCC1 mRNA and protein expression levels were measured predominantly from formalin fixed and paraffin embedded tumor tissues of NSCLC patients. It was reported that high levels of ERCC1 mRNA were significantly associated with poor overall survival (OS) in patients treated with platinum-based chemotherapy [15]. In a different study, patients with ERCC1 negative protein status showed increased survival as compared to those patients with ERCC1 positive tumors [16]. Two studies reported that lower ERCC1 protein levels were significantly associated with an increased response rate to platinum-based chemotherapy [17, 18]. In a randomized multicenter Phase III trial, patients with adenocarcinoma and negative ERCC1 protein expression had greater cisplatin sensitivity [19].

In a recent review, the association among ERCC1 SNPs, expression levels, and treatment response in SCLC was also discussed [20]. It was concluded that molecular markers based on ERCC1 might not be used for predicting treatment response in

Table 1 ERCC1 and clinical outcome of lung cancer

References	ERCC1 variable	Population	Sample size	Therapy	Outcomes
[13]	*ERCC1* SNPs *C354T* and *C8092A*	NSCLC	115	Cisplatin- or platinum-based chemotherapy	SNPs 354 C to T and SNP 8092 C to A was associated with increased or decreased treatment response
[14]	*ERCC1* SNP *C8092A and XRCC1*	Never-smokers with lung adenocarcinoma; stages IIIB/IV	158	Gefitinib or gemcitabine plus cisplatin	Patients with 8092CA genotype
[15]	ERCC1 mRNA expression	NSCLC	100	Platinum-based doublet chemotherapy	Higher expression was associated with poor overall survival (OS)
[16]	ERCC1 protein expression	NSCLC	163	Carboplatin and gemcitabine	Negative ERCC1 was associated with better survival in men but not in women
[18]	ERCC1 protein expression	NSCLC; stages IIIB/IV	170	Carboplatin and gemcitabine	Lower ERCC1 was associated with better response
[19]	ERCC1 protein expression	NSCLC	443 (264 with ERCC1 data)	Platinum-based doublet and triplet chemotherapy	Negative ERCC1 interacts with adenocarcinomas in longer survival
[17]	ERCC1 protein expression	NSCLC; International Adjuvant Lung Trial	784	Adjuvant chemotherapy with cisplatin plus vindesine or vinblastine or vinorelbine or etoposide	Patients with low ERCC1 benefit from adjuvant chemotherapy; ERCC1 was marginally prognostic for survival

SCLC patients due to a lack of clinical evidence from larger studies. Therefore, it is important for investigators to focus on studying response to chemotherapy with various molecular markers in large clinical trials of SCLC.

3 ERCC1 and Clinical Outcome of Ovarian Cancer

It is estimated that in the year of 2011, ovarian cancer will be newly diagnosed in 21,990 women and result in 15,460 deaths [12]. The standard therapy for women with ovarian cancer is primary aggressive cytoreductive surgery followed with adjuvant platinum and taxane-based chemotherapy [21, 22]. Despite efforts to provide optimal surgical management and improve adjuvant therapies, ovarian cancer remains the deadliest gynecologic cancer. Approximately 60–80 % of women diagnosed with ovarian cancer will respond to initial therapy and enter clinical remission. Another subset of women will demonstrate clinical progression during treatment and will have platinum-refractory disease. Some women who have a clinical response initially will subsequently have disease recurrence within the first 6 months following completion of therapy and demonstrate platinum resistance [23].

The success of chemotherapy is limited by the ability of an agent to target and kill cancer cells. Platinum resistance is a primary mechanism responsible for the limitations in treatment and limited survival of ovarian cancer. Up-regulation of several DNA repair pathways may contribute to platinum resistance and ultimate failure of therapy in the clinical setting, such as DNA mismatch repair, base excision repair, and NER. ERCC1–XPF heterodimers are DNA repair proteins essential for both NER and DNA cross-link repair pathways. Thus, ERCC1–XPF heterodimers are absolutely required for the repair of all types of platinum induced DNA damage [23]. Numerous studies have been conducted with aims to discover the clinical significance of ERCC1 and the NER pathway in ovarian cancer, among them are those listed in Table 2.

In a small study of 60 epithelial ovarian cancer (EOC) cases who received initial cytoreductive surgery, followed by six cycles of platinum based chemotherapy, there was an association between the *ERCC1* SNP *118 CT/TT* genotypes and platinum resistance; however, there was no significant association with overall survival in this cohort [24]. In 178 EOC cases who received platinum-based chemotherapy, patients with higher ERCC1 expression or the CC genotype may benefit from platinum plus paclitaxel, while low ERCC1 or the *C/T* or *T/T* genotype may respond well to platinum without paclitaxel [25].

Two latter studies continued to investigate *ERCC1* SNPs *C118T* and *C8092A*. In 2008, the Gynecologic Oncology Group (GOG)-172 clinical trial comparing paclitaxel/cisplatin IV to paclitaxel/cisplatin IV/IP demonstrated that again that codon 118 SNP was not associated with overall survival (OS) or progression free survival (PFS). However, the codon 8092 *CA/AA* genotypes were associated with worse PFS and OS [26]. In contrast, subsequent investigation within the GOG-182 protocol, which is a randomized trial of carboplatin, paclitaxel, gemcitabine, pegylated liposomal

Table 2 ERCC1 and clinical outcome of ovarian cancer

References	ERCC1 variable	Patient population	Sample size	Therapy	Outcomes
[24]	*ERCC1* SNP *C118T*	Adequately staged EOC, all stages	60	Carboplatin and paclitaxel	SNP 118 *CT/TT* genotypes can predict platinum resistance but not OS
[25]	*ERCC1* SNP *C118T*	Stage I–IV EOC	178	Platinum-based chemotherapy with cisplatin or carboplatin IV +/− paclitaxel IV	Higher ERCC1 or the *CC* genotype may benefit from platinum + paclitaxel, while low ERCC1 or the C/T or T/T genotype may respond well to platinum without paclitaxel
[26]	*ERCC1* SNPs *C118T* and *C8092A*	Optimally reduced, stage III EOC (GOG 172)	233	Paclitaxel and cisplatin IV or paclitaxel and cisplatin	SNP 118 was not associated with OS and PFS. The codon 8092 *CA/AA* genotypes were associated with worse PFS and OS
[23]	*ERCC1* SNPs *C118T* and *C8092A*	Optimally or suboptimally reduced patients with stage III–IV EOC (GOG 182)	280	Carboplatin, paclitaxel IV, gemcitabine, pegylated liposomal doxorubicin, and topotecan	SNP 118 *CT/TT* genotypes were associated with better survival in patients treated with platinum and paclitaxel based chemotherapy
[27]	ERCC1 mRNA in leukocytes	Optimally reduced, stage III EOC (GOG 158)	170	Paclitaxel and cisplatin IV or paclitaxel and carboplatin	ERCC1 in leukocytes is not associated with PFS or OS
[29]	ERCC1 protein expression	Chemotherapy naïve patients with stage I–IV EOC	101	Carboplatin and paclitaxel IV	Platinum resistance found in 75 % of tumors with positive ERCC1 protein expression
[28]	ERCC1 protein expression	High-grade serous adenocarcinoma stage III–IV	77	Platinum based chemotherapy with cisplatin or carboplatin	ERCC1-negative tumors have better OS

EOC Epithelial ovarian cancer, *OS* overall survival, *PFS* progression free survival

doxorubicin, and topotecan in various regimens IV, identified that SNP 118 *CT/TT* genotypes were associated with better survival in patients treated with platinum and paclitaxel-based chemotherapy [23]. Differences in route of administration, type of regimen, stage of disease, race, stage of residual disease, study designs, and end points may explain, at least in part, the conflicting results between studies.

In addition to SNPs, *ERCC1* gene expression was evaluated using mRNA isolated from peripheral blood leukocytes as a surrogate marker in GOG-158 clinical trial, which is a randomized clinical trial of 170 women with EOC comparing paclitaxel with carboplatin vs. cisplatin as initial adjuvant chemotherapy. There was no association between ERCC1 expression and PFS or OS. However, tumor tissue was not available in this study to assess direct *ERCC1* expression, and the authors stated that mRNA expression of *ERCC1* in peripheral leukocytes may not be a reliable surrogate marker in understanding the influence of the *ERCC1* gene and its effect on chemotherapy resistance and patient survival [27].

Two other studies evaluated ERCC1 protein expression to understand the specific genetic foci responsible or representative of the influence that ERCC1–XPF heterodimers have upon clinical relevance in ovarian cancer [28, 29]. The first study performed immunohistochemistry for ERCC1 protein in chemotherapy naïve patients with stage I–IV EOC and then followed outcomes after they received six cycles of platinum based chemotherapy. They demonstrated that platinum resistance was present in 75 % of tumors with positive ERCC1 protein expression [29]. Similarly, the results from the second study also showed that ERCC1 protein level was associated with OS [28].

With limited literature, it is still unclear the exact clinical usefulness of ERCC1 in EOC. It has been identified that the ERCC1–XPF heterodimer is an integral part of the NER pathway, and that this pathway affects the response to platinum-based chemotherapy in EOC. However, the appropriate target for ERCC1 evaluation which will allow for integration of ERCC1 in treatment planning is yet to be clearly identified. Further research is necessary to identify pathways in which ERCC1 can alter components of the pathway resulting in an impact on effective tailored therapy for patients with EOC.

4 ERCC1 and Clinical Outcome of Other Cancers

ERCC1 genotype has been shown to be an effective biomarker to predict the efficacy of chemotherapy for various types of cancer and chemotherapy regimens (Table 3). The results from two studies showed that the ERCC1 118 SNP was associated with efficacy of oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer [30, 31]. In a phase II clinical trial of variations of FOLFOX treatment regimens, the ERCC1 118 CC genotype was correlated with a longer PFS [30]. In the second study of 113 patients with metastatic colorectal cancer, analysis for correlation between genotype and clinical response showed that patients with polymorphism C/T in ERCC1-118 showed higher ERCC1 mRNA concentrations

Table 3 ERCC1 and clinical outcome of multiple cancers

References	ERCC1	Patient population	Sample Size	Therapy	Outcomes
[30]	*ERCC1* SNP *C118T*	Metastatic colorectal cancer	118	FOLFOX	118 C/C genotype was associated with better PFS
[31]	*ERCC1* SNP *C118T*	Metastatic colorectal cancer	113	Oxaliplatin and 5 fluorouracil, FOLFOX4 and xelox regimens	118 C/T genotype displayed higher ERCC1 mRNA and more resistance to oxaliplatin
[34]	ERCC1 mRNA expression	Locally advanced bladder cancer	108	1. Cisplatin + methotrexate 2. Methotrexate + vinblastine + epirubicin + cisplatin	Higher ERCC1 mRNA expression was associated with reduced PFS for both groups
[32]	ERCC1 protein expression	Gastroesophageal cancer	142	Epirubicin + cisplatin + 5-FU, or epirubicin + cisplatin + capecitabine before surgery	ERCC1 expression was associated with poor disease-specific ($P = 0.020$) and OS
[33]	ERCC1 protein expression	Pancreatic adenocarcinoma	95	Pancreaticoduodenectomy with adjuvant chemotherapy	Higher ERCC1 expression was associated with lower PFS and OS in 73 patients who underwent adjuvant chemotherapy

and more resistance to oxaliplatin treatment. Also, a combination of the C/C SNP in *ERCC1*-118 and Arg/Arg in XRCC1-399 correlated to better treatment response than either one of those polymorphisms alone [31].

A study of 142 cases with gastroesophageal cancer treatment with platinum-based chemotherapy drugs aimed to correlate the expression of several genes involved in DNA repair, including ERCC1, with the clinicopathological outcomes of treatment [32]. This study used tumor regression grade (TGR) as a means of analyzing clinicopathological response. TGR1 is complete regression and TGR2 shows the presence of rare residual cancer cells scattered through the fibrosis. TGR3 showed a slightly greater number of residual cells than TGR2. TRG4 showed residual cancer outgrowing fibrosis and TGR5 showed the absence of any regression. Results showed that positive ERCC1 expression correlated with negative treatment response (TGR4 or 5) and ERCC1 negative cases showed significantly greater median disease specific survival than ERCC1 positive cases and significantly greater overall survival than ERCC1 positive cases. The results suggest that tumor regression and ERCC1 nuclear protein expression are promising predictive markers in gastroesophageal cancer patients receiving neo-adjuvant platinum-based chemotherapy [32].

ERCC1 has been shown to be a potential prognostic marker for disease progression in pancreatic adenocarcinoma [33]. There was differential ERCC1 expression in pancreatic adenocarcinoma using immunohistochemistry and it was assessed as a prognostic marker for disease progression. Ninety-five pancreatic adenocarcinoma patients who underwent pancreaticoduodenectomy with available tissue samples were used ERCC1 expression analysis, PFS, and OS. The study results showed that pancreatic adenocarcinoma displayed differential levels of ERCC1 and higher levels of ERCC1 expression were associated with lower PFS and OS [33].

ERCC1 expression levels was evaluated in 108 bladder cancer patients participating in a Phase III clinical trial of an adjuvant cisplatin based chemotherapy including methotrexate [34]. The study sought to determine the usefulness of ERCC1 expression as a predictive biomarker and whether the effect as a biomarker varies with the type of chemotherapy used. Patients in the study received either CM regimen consisting of cisplatin and methotrexate, or M-VEC regimen consisting of methotrexate, vinblastine, epirubicin, and cisplatin. Results showed that lower ERCC1 levels correlated with greater PFS and higher ERCC1 levels correlated with disease progression [34]. No significant difference was found between effects of ERCC1 levels in each chemotherapy regimen independently.

5 ERCC1–XPF as Cancer Therapeutic Target

It has been well established that DNA repair pathways can enable tumor cells to survive DNA damage that is induced by chemotherapeutic or radiation treatments; therefore, inhibitors of DNA repair pathways might prove efficacious when used in combination with DNA-damaging chemotherapeutic drugs. In addition, deficient

DNA repair pathways that arise during carcinogenesis can drive some cancer cells reliant on limited DNA repair pathways for survival. Therefore, DNA repair inhibitors to target these pathways in such tumors could prove useful as single-agent therapies with selective efficacy and fewer side effects. In addition, DNA repair inhibitors can also be used in combination with DNA-damaging anticancer agents to increase the efficiency of the cancer treatment by inhibiting DNA repair pathway(s) critical for removing toxic DNA damages.

Earlier clinical studies suggest that platinum-DNA adduct may be an important biomarker for the biological effect of platinum-based chemotherapy. DNA repair particularly NER plays an important role in treatment response and resistance to platinum-based chemotherapeutic agents. One critical gene within NER pathway is the *ERCC1* gene. Data exist in multiple human cancer sites that *ERCC1* SNPs and/or expression may serve as useful biomarkers in predicting clinical outcome when platinum-based chemotherapy is utilized. Furthermore, the ERCC1–XPF complex is also involved in HR of DSBR, ICL repair, and telomere maintenance. Therefore, the ERCC1–XPF complex makes an attractive biomarker in predicting clinical outcome in cancer patients as well as a novel treatment target in chemo- and/or radiation sensitization.

Resistance to several chemotherapy drugs has been previously correlated with the over expression of both the ERCC1 and XPF proteins. These proteins form a heterodimeric endonuclease complex, which is recruited to DNA through a secondary interaction between ERCC1 and the XPA protein. Although ERCC1 is a potential anticancer drug target, it does not have intrinsic enzymatic activity. Therefore, modulation of ERCC1 might be less desirable than understanding the clinical relevance of protein–protein interactions within the NER pathway or between ERCC1 and other repair pathways, as potential targets for improving the efficacy of chemotherapy drugs.

ERCC1 expression can be suppressed by emodin, a tyrosine kinase inhibitor, which is a natural anthraquinone derivative isolated from the roots and rhizomes of numerous plants [35]. In addition to suppressing ERCC1 expression, the cytotoxicity to capecitabine can be enhanced by emodin by down-regulating the expression of Rad51 and up-regulation of thymidine phosphorylase expression [36]. In human tongue cancer cells, emodin treatment induced DNA damage and inhibited DNA repair-associated gene expression, including ATM, ATR, 14-3-3sigma, BRCA1, DNA-PK, and MGMT [37]. This inhibitory effect is supported by the previous observation that epidermal growth factor up-regulate ERCC1 through MAPK (ERK1/2) signaling [38]. Moreover, inhibition of HER2–PI3K–AKT signal pathway down-regulates ERCC1 that may contribute to the synergism between trastuzumab and chemotherapy [39].

Three marine-derived NER inhibitors, trabectedin (Et743; Yondelis), PM01183, and PM00104 showed enhanced activity toward cisplatin- and oxaliplatin-resistant ovarian carcinoma cells or Ewing's sarcoma cell lines [40, 41]. In addition to its function as a DNA repair inhibitor due to drug-related DSBs and adduct formation, trabectedin treatment also results in perturbation in the transcription of inducible genes, such as the multidrug resistance gene MDR1.

ERCC1–XPF involved in different repair pathways through specific protein–protein interactions and selective disruption of these interactions can influence different repair pathways separately. UCN-01 (7-hydroxystaurosporine) has been developed as an anticancer agent that potentiates cisplatin and carboplatin toxicity (demonstrated in preclinical models and a phase I clinical trial, respectively), which has been shown to interfere with the interaction of ERCC1 and XPA [42]. The XPA-binding domain of ERCC1 is required for NER only but not other DNA repair pathways [43]. It is not clear whether this specificity may have limitation considering other repair pathways may serve as the backup mechanisms to remove chemotherapeutic agent-induced DNA damages.

6 Conclusions and Future Prospective

The ERCC1–XPF complex has been evaluated as a biomarker in predicting clinical outcome as well as a potential treatment target. In multiple cancer sites (e.g., lung, ovarian, colorectal, etc.) higher levels of ERCC1 mRNA/proteins correlate with poor clinical outcome and resistance to platinum-based chemotherapies. The *ERCC1* SNP at codon 118 leads to a C:T substitution that may influence mRNA/protein levels, DNA repair capacity, and treatment response. The upstream promoter region (around 410 base pairs) to the *ERCC1* initiation site contains a variety of transcription factor binding sites for GATA-1, p53, AP-1, c-Jun, JunB, ER-α, and NF-κB1; they may contribute to ERCC1 expression regulation and resistance to cisplatin.

The potential application of inhibitors of ERCC1 expression or protein–protein interactions in cancer therapy is starting to become apparent. Several approaches have shown promising clinical applications. First, ERCC1 expression can be suppressed by emodin, a tyrosine kinase inhibitor to enhance sensitivities to different chemotherapeutic agents. Second, three marine-derived NER inhibitors, trabectedin (Et743; Yondelis), PM01183, and PM00104 showed enhanced activity toward cisplatin- and oxaliplatin-resistant ovarian carcinoma cells or Ewing's sarcoma cell lines. Third, UCN-01 has been developed as an anticancer agent by targeting the interaction between ERCC1 and XPA to potentiate cisplatin and carboplatin toxicity.

Selective inhibitions of DNA repair pathways have the potential to sensitize chemotherapeutic drugs; synthetic lethality is another potential application of DNA repair inhibitors in tumor with defective DNA repair for selective tumor cell killing. Considering the involvement of ERCC1 in multiple DNA repair pathways critical for repairing DNA damages induced by a variety of chemotherapeutic agents used for human cancers, future development of ERCC1 inhibitors as single or combination treatment may have a great impact on designing new and more effective cancer therapies.

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