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Nucleotide excision DNA repair pathway as a therapeutic target in patients with high-risk diffuse large B cell lymphoma

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Diffuse large B-cell lymphoma (DLBCL) is the most frequent type of non-Hodgkin lymphoma. DLBCL is a molecularly heterogeneous disease, and the addition of Rituximab to combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) has significantly improved the survival of patients.[1]

Gene expression profiling studies revealed that DLBCL comprises two main subgroups displaying distinct molecular gene signatures and clinical outcome: one subgroup, termed germinal-center B-cell-like (GCB), associated with a gene expression profile (GEP) of healthy germinal-center B cells and with a good outcome, and another subgroup, termed activated B-cell-like (ABC), with GEP of healthy peripheral blood activated B cells and with a poorer outcome. GCB and ABC subgroups represent 50% and 30%, respectively, of DLBCL cases. The residual 20% of patients are unclassifiable.[1]

We used previously described methods to build powerful risk scores in hematological malignancies and designed a 12-gene expression-based risk score (GERS) predictive for overall survival (OS) in two independent cohorts of patients with DLBCL.[2] GERS allows identifying 12.3% of patients within GCB and high risk and 33.7% of patients within ABC and high risk. GERS is an independent prognostic factor when compared with previously published factors, including the International Prognostic Index (IPI).[2]

Of interest, GERS allows identifying high-risk patients with a median OS of 24.6 and 14.3 mo when treated with CHOP or R-CHOP regimen, respectively.[2]

GERS high-risk patients are characterized by a significant enrichment, in tumor samples, of genes coding for nucleotide excision DNA repair (NER) pathway, including ERCC2/XPD, ERCC3/XPB, ERCC4/XPF, ERCC6/CSB, ERCC8/CSA, DDB2 and polymerase delta.[2]

Cyclophosphamide is a nitrogen mustard derivate that induces interstrand crosslinks (ICLs). Doxorubicin has been shown to intercalate into DNA, poisoning the transient topoisomerase II-DNA intermediate formed during transcription and replication, resulting in a double-strand DNA break (DSB). Other effects of doxorubicin treatment have been reported, including free radicals release, DNA adducts and formaldehyde-dependent ICL formation. Opening of the two strands of DNA helix is mandatory for DNA replication and transcription. ICLs are extremely toxic to cells, because they block DNA helix opening due to chemical reactions involving bases of opposed strands, resulting in irreversible covalent linkage. This overexpression of NER pathway genes could be associated with CHOP chemotherapy resistance in DLBCL patients. In cancer cells exposed to DNA damaging agents, NER play a key role in removal and repair of the DNA damages, thus protecting cancer cells from death.[3] It has been demonstrated that NER is a major DNA repair mechanism that removes cisplatin-induced DNA damages, and that resistance to platinium-based therapy in solid tumors correlates with high expression of ERCC1, a key element of the NER machinery. NER removes helix-distorting adducts on DNA and contributes to the repair of ICLs (**Fig. 1A and B**). The xeroderma pigmentosum proteins (XP) and ERCC1 play crucial roles in both ICL and DNA adducts repair pathways. Furthermore, NER deficiency is associated with a reduced capacity to repair ICL and a higher sensitivity to platinium agents.[3] The NER machinery overexpression in DLBCL patients with poor outcome could participate in CHOP treatment tumor cells escape (**Fig. 1A and B**).

Targeting NER pathway could have therapeutic interest in high-risk patients, as defined by GERS, to reverse resistance to CHOP regimen. Currently, there is no specific inhibitor of NER pathway available. However, previous studies reported that cyclosporine A could downregulate XPA and XPG protein expression and cetuximab could inhibit XPF protein expression in colorectal cancer cells.[4] F11782, a novel dual catalytic inhibitor of topoisomerases I and II, was also described as a potent inhibitor of NER.[2] Recent study reported a virtual screening against the ERCC1-XPA interaction and identification of novel inhibitors that block the XPA-ERCC1 binding.[5] Furthermore, these compounds significantly sensitize colon cancer cells to UV radiation, indicating inhibition of NER.[5]

It was also reported that PARP activation following UV radiation exposure promotes association between PARP1 and XPA, a central protein in NER.[6] PARP1 association with XPA and UV radiation-stimulated XPA chromatin association are inhibited by PARP inhibitors.[6]

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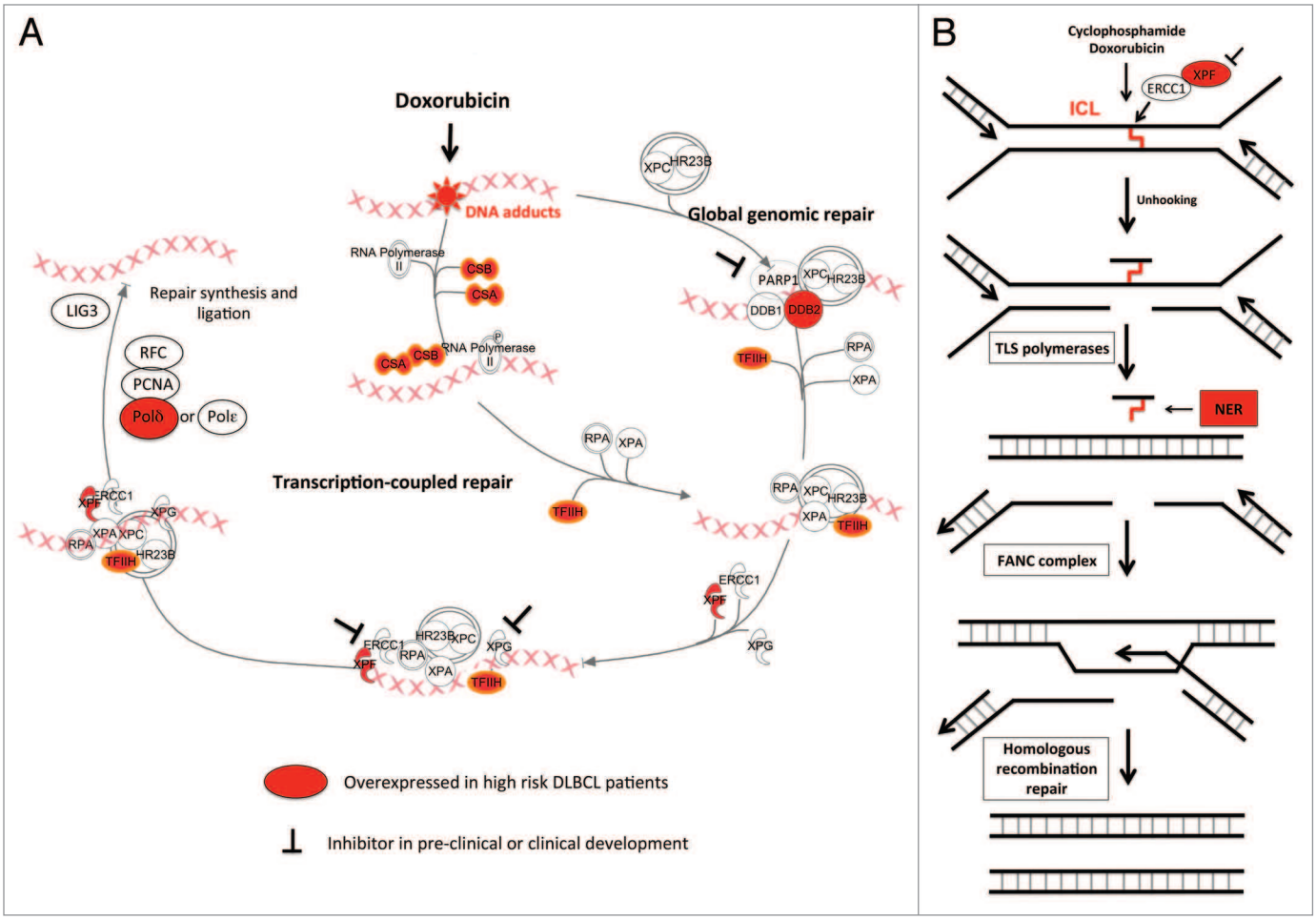

Figure 1. Potential roles of NER in DLBCL cells chemoresistance. (**A**) Doxorubicin induced DNA adducts: Repair of DNA adducts by transcription-coupled NER or by global genomic NER differs in their initial steps. Transcription-coupled NER involves Cockayne syndrome WD repeat protein A (CSA) and CSB, whereas in global genomic NER recognition is dependent on XPC-HR23B and DDB proteins. XPA, replication protein A (RPA) and TFIIH are involved in both pathways. Thereafter, the steps are common, with excision of the damaged oligonucleotide by XPG and ERCC1-XPF, then resynthesis of the intact oligonucleotide and ligation are accomplished by DNA polymerase-δ or polymerase-ε and DNA ligase 3 (LIG3). (**B**) Cyclophosphamide or doxorubicin induced ICLs: Progression of replication forks will be blocked by ICL. Stalled replication forks triggers surveillance mechanisms and the initial event, the incising of ICLs by serial or combined activities of XPF-ERCC1 and MUS81-EME1. These nucleases cut one strand of the damaged DNA, unhooking the ICL and leaving a gap that is bypassed by translesion synthesis polymerases (TLS). NER removes monoadducts and repairs the gap. The remaining DSB is repaired by homologous recombination repair.

More recently, PARP inhibition or specific depletion of PARP-1 was shown to decrease the efficiency of UV-induced DNA damage removal from human skin fibroblasts.[7] PARP1 could interact with DDB2 in the local area of UV-damaged chromatin and PARP inhibition abolishes UV-induced interaction of DDB2 with PARP1 or XPC and also the localization of XPC to UV-damaged DNA (**Fig. 1**). Taken together, these data demonstrate PARP1 collaborates with DDB2 to increase the efficiency of the lesion-recognition step of global genomic NER pathway.[7]

Multiple clinical trials have been initiated using a collection of PARP inhibitors in solid tumors.[8] Clinical-grade PARP inhibitors, in combination with CHOP chemotherapy, could be of clinical interest in the high-risk group of DLBCL patients identified with GERS.

In conclusion, GERS makes it possible identifying patients with high-risk DLBCL, who will be refractory to CHOP-based regimens. Inhibitors of the NER pathway have the potential of reversing drug resistance and improving the efficacy of treatments in DLBCL.

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