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DNA double strand breaks-repair – related synthetic lethality – molecular basis and application in anticancer therapy

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Abstract
Personalized anticancer therapy takes into consideration molecular changes unique for each cancer case and attempts to identify the therapy which will eliminate neoplastic cells the most efficiently with minimal side effects. Cancer cells carry multiple changes resulting in genomic instability responsible for accumulation of further modifications in their genome and tumor progression. Loss of the gene which product takes part in the pathway essential for cell survival (e.g. DNA repair) forces cancer cells to become "addicted" to alternative pathways. This phenomenon of dependence on the secondary trail could become a tool for personalized anticancer therapy. Synthetic lethality exploits "addiction" of cancer cells to

changes formed on the pathway of carcinogenesis by inhibition of genes and proteins crucial for the alternative pathways responsible for cancer cell survival. These changes, missing in the genome of normal cells and tissues cause them to evade lethal influence of compounds used in the induction of synthetic lethality in neoplastic cells. Research on this phenomenon is conducted within multiple cellular pathways. Synthetic lethality approaches taking advantage of alterations in the mechanisms of DNA repair are very likely to have a great impact on the field of anticancer therapy. In this short review, we discuss molecular basis of synthetic lethality in the cancer cells with deficiencies in DNA double strand break repair pathways. We will also shortly review the application of these interactions in clinical use and the mechanisms of resistance of cancer cells to synthetic lethality.

Key words
DNA repair, synthetic lethality, cancer, personalized medicine, PARP inhibitors

Introduction

Our DNA is constantly exposed to the exo- and endogenous damaging factors. Exogenous threats include ionizing radiation, hypoxia or anticancer chemotherapeutics including compounds like platinum salts, alkylating agents or topoisomerase inhibitors. However, DNA damage can occur even in the absence of external damaging factors, as DNA is vulnerable to the influence of endogenous genotoxic agents and processes naturally occurring in the cell's environment. This includes generation of reactive oxygen species (ROS) during metabolism or collision of transcription or replication machinery [1]. The most toxic results of DNA damaging factors are double strand breaks (DSBs) which are disruptions of chromosome continuity. In comparison to the rapture of a single DNA strand, where the sequence can be easily rebuilt basing on the complementary, uninterrupted strand, restoring chromosome continuity and sequence order could be a challenging task. Unrepaired DSBs can result in the cell death and lead to an increase in genomic instability by causing genome rearrangements, mutations, loss of heterozygosity [2]. Such changes are responsible for dysregulated cell growth, tumor progression and increased tumor cell invasion. Scars arising after multiple deletions

and inversions are visible in the chromosomes of about 2-3% of cancer cells [3]. Therefore, proper functioning of DNA repair systems is crucial to prevent neoplastic transformation and guarantee genome stability.

Disruption of processes crucial for cell survival (e.g. DNA repair systems) could be potentially used as a therapy aimed against neoplastic cells. In their genome loss of the gene which product is important for cell survival is probable due to the genomic instability. Under conditions of loss of such compound, cancer cell in order to survive redirects the tasks to alternative pathway and becomes "addicted" to it. Synthetic lethality as a novel tool in anticancer therapy assumes inhibition of an alternative pathway in order to sensitize neoplastic cells and subsequently cause their death. This elegant method would let us selectively eliminate tumor cells and not normal cells and tissues, because the action of basic mechanism will rescue them from the influence of backup pathway inhibitor [4]. Development of personalized therapy basing on unique cancer cell vulnerabilities is very likely to increase the efficiency and specificity of novel anticancer treatments.

The concept of synthetic lethality in anticancer therapy

The phenomenon of synthetic lethality was first ascribed by Theodor Dobzhansky in 1922, however the revolutionary idea of using it in anticancer therapy was published in 1997. Leland H. Hartwell characterized it as a method of a great medical potential which could also help to identify network of interactions underlying carcinogenesis [5, 6]. In the process of carcinogenesis normal cells gradually turn into cancerous, invasive derivatives. They become self-sufficient in growth signals induction which results in increased proliferative potential and invasive character of cancer cells. They also evade proapoptotic and growth suppressing signals [7]. Changes occurring in the genome of neoplastic cells often become the origin of the "addiction" of their viability to function redirection to backup pathways. Depending if neoplastic cell becomes addicted to the oncogene or gene that itself is not classified as oncogene but still supports cancerous phenotype and provides its survival, the phenomenon is called either "oncogenic" or "non-oncogenic addiction" [8]. Unique changes of the cancer cell's genome are the features allowing to design therapy which would specifically distinguish them from normal tissues. Targeting pathways buffering the loss of mechanisms essential for cell survival sho-

uld create a specific therapy giving minimal side effects. Abnormalities in DNA damage response systems predispose to neoplastic transformation and determine the cell response to the therapy. Tumor-specific defects of repair mechanisms seem to be an ideal target for such therapy as they share similarities in the order of the stages and some proteins create networks of interactions between multiple systems which may mean that many synthetic lethality connections may exist within them[9].

Double strand break classical and alternative repair pathways

The main systems responsible for repair of DSBs are homologous recombination (HR) and non-homologous end joining (NHEJ) and their two subpathways. HR is considered error-free but it works basing on the template of extensive homologous sequence of sister chromatid or homologous chromosome which means it can be functional only during G2/S phases when the proximity between homologous sequences is the smallest [10]. NHEJ on the other hand does not need long fragments of homology and can work on the blank or near blank ends or use microhomology between short ssDNA overhangs. However, NHEJ repair may contribute to the genomic instability because substrate strands might not be chosen properly resulting in translocations and end-editing process may lead to deletions and insertions [11]. In the first step of canonical or classical NHEJ (cNHEJ), the damage is recognized and bound by Ku heterodimer (Ku70/Ku80) which protects ends from nucleolytic attacks. Ku serves as a loading factor which recruits different agents needed for lesion repair. When bound to DNA, Ku shows high affinity to the catalytic subunit of DNA-dependent protein kinase (DNA-PKcs). Interactions between them result in activation of DNA-PK complex, binding it at each end and tethering them. Phosphorylation of different residues of DNA-PK results in either opened or closed lesion conformation which either blocks or allows different proteins like end-processing proteins, polymerases or ligases to the damage area [12]. The crucial moment of cNHEJ is performed by ligase IV (LIG4) in cooperation with X-ray repair cross-complementing protein 4 (XRCC4) which aligns and stabilizes ends for final end joining[13]. Abnormalities in the proper functioning of cNHEJ caused for the instance by mutations in Ku, DNA-PKcs or LIG4 may lead to the redirecting of DSBs repair to the alternative mechanism – altNHEJ. Such incident may lead to formation of translocations and more extensive de-

letions due to the more inaccurate character of backup NHEJ pathway. Under physiological conditions altNHEJ does not exhibit any significant role. In comparison to cNHEJ, its backup pathway requires microhomology between single stranded overhangs on lesions ends. One of the reasons of error-prone character of this repair system is its lower kinetic often leading to the damage ends separation, selection of wrong partners for repair and genome rearrangements. End-resection required for microhomology searching may result in relatively long deletionsand loss of DNA between homologous fragments [14]. AltNHEJ, similarly to the basic mechanism, begins with the step of damage recognition and binding by repair machinery which in this case is held by Poly [ADP-ribose] polymerase 1 (PARP1). Because of the wide variety of processes which PARP participates in (including induction of HR at stalled replication forksand repair of DNA base modifications and single strand breaks in base excision repair BER) it is lately being extensively researched as a target for anticancer therapy in cases with detected deregulations of processes like HR or cNHEJ. To this day, correlation between mutation in BRCA gene and inhibition of PARP is the only one which already found application in anticancer therapy and is currently being widely researched in multiple clinical trials. In altNHEJ, PARP participates in formation of the synapsis between ends and recruits different factors like microhomology revealing complex MRN (MRE11/RAD50/NBS1). Further steps of repair include microhomology annealing by polymerase Θ and end ligation held by either LIG1 or complex of LIG3a and X-ray repair cross-complementing 1 protein (XRCC1) [15].

In comparison to NHEJ, HR system requires extensive homology revealing what ensures its high accuracy in reconstruction of the DNA sequence. HR involves steps of end processing which similarly to altNHEJ is held by MRN complex but further resection is maintained by exonuclease 1 (EXO1). Created single stranded DNA overhangs are protected by replication protein A (RPA) which particles cover strands like beads. In the next step recombinase filament of RAD51 forms at the end of the lesion and invades homologous sequence[16]. Tumor suppressor proteinsBRCA1 and BRCA2 are other elements crucial for proper functioning of HR system by interaction with compounds like MRN or RAD51. The ability of BRCA2 to bind both ss-, dsDNA as well as RAD51 may indicate its important role in the proper localization and formation of the recombinase

filament [17]. BRCA1 and 2 are bound together by PALB2 (partner and localizer of BRCA2) which also stabilizes them and helps them localize at the lesion. The last protein supporting recombinase filament is RAD54 which cooperates with it at the stages of homology search, D-loop formation and catalyzes its dissociation from heteroduplex. Elongation of the damaged strand localized in D-loop is led on a template of homologous sequence and when the process is over it dissociates and pairs with elongated overhang at the other end of a damage. Excessive nucleotides at the 3' ends of freshly synthetized sequences are then removed to prepare ends for ligation [18].

RAD52 is a protein participating in HR repair, promoting binding of recombinase complex to RPA coated DNA mainly by abolishing RAD51--binding inhibitory effect of RPA-ssDNA complex [19]. It has been proposed that recombination mediators RAD52 and BRCA1/2 take part in separate HR subpathways. Basic mechanism depends on action of BRCA together with RAD51 as it was described above but under conditions of BRCA depletion, alternative pathway depending on RAD52/RAD51 activates. It has been shown that cancer cells carrying mutations of BRCA resulting in loss or reduction of their activity were sensitive to inhibition of RAD52 [20].

Synthetic lethalityclinical application

Addiction to the elements crucial for repair of DSB is a frequent phenomenon in cancer cells with abnormalities in basic repair systems. Such systems become vulnerabilities which may be utilized in synthetic lethality-related therapy which could sensitize tumor to DNA damage accumulation. This elegant approach aims genomic changes specific for cancer cells and not normal cells which provides its high specificity, satisfactory results at low doses and limited side effects [21]. Research over network of interactions between DSB repair compounds have made it possible to forecast targets for synthetic lethality based anticancer therapy.

Synthetic lethality interactions between PARP1 and BRCA are the only ones which are clinically significant for the present moment. Evidence of response of BRCA1/2 deficient cells to PARP inhibitors were first reported in 2005 [22]. Proteins from PARP family are involved in pathways like repair of single strand breaks and base modifications in BER/SSBR mechanism, repair of DSBs in altNHEJ under conditions of

disrupted cNHEJ or HR initiation at stalled replication forks. Mice deprived in PARP are viable and fertile, however, they become sensitive to factors damaging DNA (e.g. alkylating agents or radiation) [23]. Inactivation of PARP results also in an unsuccessful repair of single strand breaks which results in their progression to DSBs and accumulation under conditions of insufficient activity of DSB repair mechanisms (e.g. BRCA1/2 mutations) [24]. Although NHEJ is considered major DSB repair pathway in mammalian cells, some cancer types rely more on mechanisms requiring homology [25]. Mutations in BRCA1/2 or their epigenetic silencing termed "BRCAness" have been associated with elevated risk of ovarian and breast cancer. Abnormalities in BRCA genes have been also identified in cases of melanoma, prostate and pancreatic cancers [26]. Translocation BCR-ABL1 in leukemia was correlated with downregulation in BRCA1 to extremely low level which was due to suppressed translation [27]. PARP inhibitors can potentially be utilized under such conditions and sensitize cells to lethal effect of DNA lesions. The conditions of BRCA-deficiency in cells not expressing abnormalities in BRCA structure or level could be achieved by local mild hyperthermia leading to regional BRCA2 degradation [28].

Currently only a few PARP inhibitors found clinical application in personalized anticancer therapy although efficiency and specificity of novel compounds is investigated in numerous clinical trials. The group of PARP inhibitors includes olaparib (AZD2281, Lynparza™), rucaparib (AG14699, Rubraca®),niriparib (MK4827, Zejula™) already approved by Food and Drug Administration (FDA) as well agents like veliparib (ABT888), talazoparib (BMN673) or CEP9722 which are under clinical investigation in monotherapy and in combination with other DNA damaging compounds enhancing their effect [29]. PARP inhibitors were designed to mimic NAD+, bind to the donor residue of PARP and reduce its activity. Due to the high degree of homology between NAD-binding domains of members of PARP proteins family, inhibitors are unable to recognize different isoforms and they more likely influence the whole group of factors [30]. Novel inhibitors used in PARP aimed therapy demonstrate better pharmacokinetics, bioavailability and allow to achieve better results at significantly lower doses in comparison to previous PARP inhibitors [31].

What is more, PARP inhibitors might find clinical application under conditions of ineffective cNHEJ repair arising as a result of disruptions

in the components essential for this pathway, e.g. LIG4 or Ku. Targeting PARP in melanoma cells expressing decreased level of LIG4 resulted in accumulation of toxic DSBs and specific elimination of tumor cells [32]. Acute myeloid leukemia (AML) cells carrying internal tandem duplications in fms related tyrosine kinase 3 (FLT3) gene demonstrate reduced level of Ku proteins and increased level of LIG3α. Under such conditions, altNHEJ, and not cNHEJ, is the major mechanism involved in the repair of DSBs and genomic rearrangements like deletions are more likely to occur. Utilization of PARP inhibition under conditions of low level of Ku could potentially sensitize leukemia cells carrying internal tandem duplications in FLT3 gene [33].

What is more, further efforts are made to identify and utilize other networks of interactions between factors essential for DSB repair. Previously mentioned crosstalk between two HR subpathways – BRCA1/2--RAD51 and RAD52-RAD51, might become the next target for synthetic lethality related anticancer therapy. RAD52 targeting might selectively eliminate cells harboring mutations of genes like BRCA1/2 or PALB2 crucial for primary HR pathway where alternative RAD52-RAD51 pathway could be active in order to grant cell survival [34].

Synthetic lethality in combination therapy

Synthetic lethality compounds were primarily used in order to sensitize cancer cells to different DNA damaging agents e.g. radiotherapy or cytotoxic compounds but recent clinical trials show their high potential also in monotherapy. For instance, in cancer cells expressing dysfunctions in HR repair inhibition of PARP resulted in chemo- and radiosensitization. Nowadays, a wide spectrum of synthetic lethality compounds is an object of extensive research over they synergistic action with different anticancer agents. PARP inhibitors like veliparib or olaparib are under clinical trials in combination therapy with radiotherapy [35].

PARP inhibitors destabilizing repair processes in HR deficient cells also compliment therapy with currently available chemotherapeutics like temozolamide or dacarbazine – alkylating agents introducing alkyl groups to DNA [36]. Unsuccessful repair of such modifications, especially the most toxic O6-methylguanine, leads to the arrest of replication forks. Such obstacle leads to the PARP1 recruitment and HR activation. Cells with decreased effectiveness of HR appear to be more sensitive to the

alkylating agents [37]. For that reason combination of alkylating agents and PARP inhibitors appears as an attractive solution and its effectiveness is currently under analysis in numerous clinical trials in many cancer types.

Another compounds demonstrating synergistic effect with synthetic lethality compounds are DNA-damaging platinum salts (cisplatin or carboplatin) or gemcitabine which inhibits DNA replication by blocking replication forks progress [38, 39]. Topoisomerase inhibitors and poisons like camptothecin, irinotecan, etoposide, doxorubicine or mitoxantrone interact with enzymes responsible for DNA relaxation by induction of breaks in either one or both strands of DNA. Topoisomerase inhibition or poisoning results in their trapping at the DNA which may lead to the collision with replication machinery. PARP inhibition synergism with topoisomerase trapping bases on the requirement of PARP activity in repair of topoisomerase inhibition-caused damage [40].

Taxanes like docetaxol or paclitaxel suppress microtubules polymerization during cell division resulting in mitosis arrest and cell death. Taxanes are used in the treatment of gastric cancer which cells often harbor mutations in ATM gene (ataxia telangiectasia mutated) that often correlates with PARP inhibition sensitivity [41].

Resistance development

The challenging problem in the clinical utilization of the synthetic lethality based therapy is the development of resistance to the inhibitors. Mutations arising in different regions of BRCA appear to effect in various intensity of protein function loss. Some mutations may lead to the complete loss of activity of BRCA, whereas other may give rise to the protein with residual activity resulting in better resistance to PARP inhibitors [42]. What is more, treatment basing on drugs inducing DNA damage or mobilize error-prone systems may result in secondary resistance due to the novel mutations in genes like BRCA restoring their function and activating basic pathways [43]. Resistance development in cancer cases without function-restoring mutations suggest presence of other mechanisms responsible for inhibitor refractory phenotype. Mutation in BRCA1 antagonist named 53BP1, along with downregulation in BRCA1/2 results in rewiring of repair processes back to HR pathway [44]. The last element of cell resistance to the synthetic lethality inhibitors might be overexpres-

sion of p-glycoprotein efflux pump (PgP) responsible for drug transport from the inside of the cell to its environment [45]. Solution of the problem of cancer resistance appears to be critical for further development of all synthetic lethality-related therapies.

Summary

Utilization of cancer cell specific vulnerabilities in synthetic lethality approach appears to be an elegant method of precise elimination of tumor cells without harm to healthy cells and tissues. Approval of inhibitors like olaparib by world agencies and further promising results from researches and clinical trials direct medicine into a new trajectory of personalized therapy and encourage further studies contributing to the broadening of our understanding on molecular biology of neoplastic diseases. However, this novel approach is still in its infancy and requires further insight into long term therapy effects and broader insight into synthetic lethality interaction networks which could find application in clinical use.

Abbreviations

altNHEJ - alternative non-homologous end joining, AML - acute myeloid leukemia, ATM - ataxia telangiectasia mutated, BER - base excision repair, cNHEJ - classical/canonical non-homologous end joining, DNA-PKcs - catalytic subunit of DNA-dependent protein, DSBs - double strand breaks, EXO1 - exonucleases 1, FDA - Food and Drug Administration, HR - homologous recombination, LIG1/3/4 - ligase I/III/IV, MRE - complex of MRE11, RAD50, NBS1, NHEJ - non-homologous end joining, PALB2 - partner and localizer of BRCA2, PgP – p-glycoprotein efflux pump, ROS - reactive oxygen species, RPA - replication protein A, ssDNA - single stranded DNA, XRCC1/4 - X-ray repair cross-complementing protein 1/4

Conflict of interest

There is no conflicts of interest.

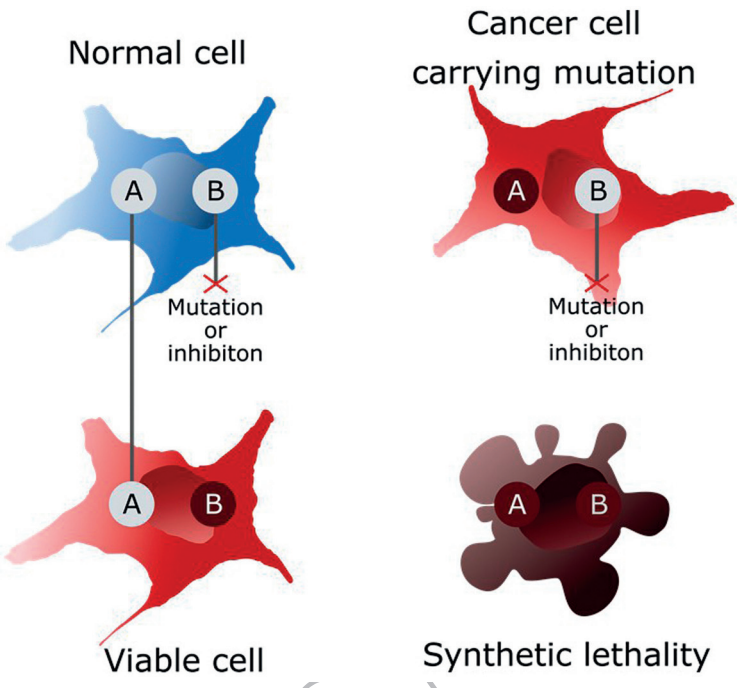

Figure 1. The concept of synthetic lethality. Normal cells possess two functional, alternative pathways of the process crucial for their survival (e.g. dependent to either gene A or B essential for these pathways). In tumor cells, genomic instability often eliminates one of the pathways (loss of function mutation in A gene) arising cell "addiction" to the alternative route. Impairment of the alternative pathway (B gene) due to the loss of function mutation or to the targeting it with inhibitor would result in cell death. Mutation or inhibition of B gene in normal cell does not significantly affect its survival, since basic pathway dependent on A gene remains functional.

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