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Department of Genetics and Microbiology

Bachelor Thesis

The Role of DNA Repair in the Onset and Therapy of Ovarian Cancer

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Prohlašuji, že jsem bakalářskou práci na téma: “The Role of DNA Repair in the Onset and Therapy of Ovarian Cancer“ vypracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

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Abstract

DNA repair and DNA damage response are very important biological systems, inevitable to maintain genomic stability and fidelity of the genetic information, for the onset of ovarian cancer. Further, DNA repair is also substantially involved in the response to the therapy, since many chemotherapeutics act as DNA damaging agents.

This literary analysis is intended to survay the relevance of DNA repair to ovarian carcinogenesis. Special emphasis is placed on repair defects, as it is inextricably associated with the onset of cancer and treatment outcome. Apart from well-known alternations in ovarian cancer susceptibility genes, such as *BRCA1* and *BRCA2* involved in homologous recombination repair, ample space will be dedicated to less common gene mutations across different repair pathways.

Research confirms that abnormalities in the proteins responsible for homologous recombination repair are the leading cause of ovarian cancer. The majority of authors also suggested that targeting DNA repair pathways, especially base excision repair, can improve chemotherapy efficiency in a synergic manner. The same applies to nucleotide excision repair, which repairs platinum-DNA adducts and thus contibutes to platinum drugs resistance emerging. By way of contrast, mismatch repair in ovarian cancer is rather poorly investigated and its deficiency is frequently related to Lynch syndrome, which predispose people to get colon as well as extracolonic cancers.

Key Words: DNA damage, DNA repair, ovarian cancer, incidence, therapy, resistence towards chemotherapy

Abstrakt

Detekce poškození DNA a její oprava jsou důležité biologické systémy, které chrání genetickou informaci před změnami a přispívají tak k celkové stabilitě genomu. Jelikož je mnoho látek užívaných v boji proti rakovině založených na vyvolávání DNA poškození, podílí se mechanizmus oprav DNA významnou měrou i na léčebné odezvě organizmu na chemoterapii.

Cílem této práce je uceleně shrnout problematiku vzniku rakoviny vaječníků ve vztahu k opravě DNA. Zvláštní důraz je přitom kladen na poruchy jednotlivých reparačních drah, které jsou neoddělitelně spjaty se vznikem rakoviny i úspěšností její léčby. Kromě nejznámějších genových mutací souvisejích s rakovinou vaječníků, jako jsou *BRCA1* a *BRCA2* účastnící se homologní rekombinace, bude značný prostor věnován i méně známým mutacím.

Nejčastějším důvodem vzniku rakoviny vaječníků jsou dle výzkumů poruchy funkce proteinů uplatňujících se v opravách DNA homologní rekombinací. Výzkumy rovněž ukazují, že cílená inhibice či poškození opravných drah DNA, zejména bázových excizních oprav, mohou napomáhat efektivnímu působení chemoterapie. To platí i pro nukleotidové excizní opravy, které odstraňují adukty platinových komplexů na DNA a napomáhají tak k ustanovení rezistence vůči platinovým cytostatikům. Mechanimus korekce správného párování bazí je u ovariálního karcinomu oproti výše zmiňovaným drahám dosud poměrně málo prozkoumán. Porucha tohoto systému je nejčastěji zmiňována v souvislosti s Lynchovým syndromem, onemocněním projevujícím se vznikem kolorektálního karcinomu a několika dalších typů rakovin včetně rakoviny vaječníků.

Klíčová slova: poškození DNA, oprava DNA, nádory vaječníků, incidence, léčba, resistence k cytostatické léčbě

Content

List of Abbreviations

A	adenine
ABC transporter	ATP-binding cassette transporter
ADP	adenosine diphosphate
AKT1	AKT serine/threonine kinase 1
AKT2	AKT serine/threonine kinase 1
AP	apurinic/apyrimidinic site
APE1	AP endonuclease 1
APEX	gene encoding AP endonuclease 1
ATP	adenosine triphosphate
BCDX2	protein complex consisting of RAD51B, RAD51C, RAD51D and XRCC2 subunits
BCL-2	gene encoding B-cell lymphoma 2 apoptosis regulator
BER	base excision repair
BRAF	gene encoding serine/threonine protein kinase B-Raf, proto-oncogene
BRAF(V600E)	mutation at codon 600 of *BRAF*, where the valine is substituted by glutamic acid
BRCA1	gene encoding breast cancer type 1 susceptibility protein
BRCA2	gene encoding breast cancer type 2 susceptibility protein
BRIP1	gene encoding BRCA1 interacting protein C-terminal helicase 1
C	cytosine
c-myc	myc proto-oncogene protein
CAK	CDK-activating kinase complex
CAV1	caveolin-1, scaffolding protein
CDK12	gene encoding cyclin dependent kinase 12
CMMRD	constitutional mismatch repair deficiency
CpG island	cytosine-phosphate-guanine island
CRC	colorectal cancer
CSA	Cockayne syndrome A protein
CSB	Cockayne syndrome B protein
CX3	protein complex consisting of RAD51C and XRCC3 subunits
DDB1	DNA damage-binding protein 1, UV-induced DNA damage recognizing protein
DDB2	DNA damage-binding protein 2, UV-induced DNA damage recognizing protein
DDR	DNA damage response
DHJ	double holliday junction
DNA	deoxyribonucleic acid
DNA2	DNA replication helicase/nuclease 2
dRP	deoxyribophosphate
DSB	double strand break
DSBR	double strand break repair
dsDNA	double-stranded deoxyribonucleic acid
e.g.	*exempli gratia*, latin phrase meaning „for example“
EC	endometrial cancer
EOC	epithelial ovarian cancer
ERCC1	excision repair cross-complementation group 1
et al.	*et alii*, latin phrase meaning „and others“
etc.	*et cetera*, latin phrase meaning „and so forth“
EXO1	exonuclease 1
FA	Fanconi anemia
FANCD2	Fanconi anemia complementation group D 2 protein
FEN-1	flap endonuclease 1
Fig.	figure

G	guanine
GADD45	gene encoding growth arrest and DNA-damage-inductible proteins, cell cycle regulators
GGR	global genomic NER
HBOC	hereditary breast and ovarian cancer syndrome
HELQ	HELQ helicase
HER-2/neu	human epidermal growth factor receptor 2
HJ	holliday junction
HNPCC	hereditary nonpolyposis colorectal cancer
HR	homologous recombination
HRR	homologous recombination repair
ICL	interstrand crosslink
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
KRAS(G12C)	mutation at codon 12 of *KRAS*, where the glycine is substituted by cysteine
LIG1	DNA ligase 1
LIG3	DNA ligase 3
LLS	Lynch-like syndrome
LS	Lynch syndrome
MAP	MUTYH-associated polyposis
MBD4	gene encoding methyl-CpG-binding domain protein 4, DNA glycosylase
MLH1	gene encoding mutL homolog 1, MMR component
MMC	mytomicin C
MMEJ	microhomology-mediated end joining
MMR	mismatch repair
MPG	N-methylpurine DNA glycosylase
Mre11	double strand break repair nuclease
MRN complex	Mre11-RAD50-NBS1 protein complex involved in initial DSB response
MSH2	gene encoding mutS homolog 2, MMR component
MSH6	gene encoding mutS homolog 6, MMR component
MSI	microsatellite instability
MutH	methyl-directed mismatch repair protein MutH
MutL	methyl-directed mismatch repair protein MutL
MutLα, MutLβ, MutLγ	forms of MutL protein
MutS	methyl-directed mismatch repair protein MutS, heterodimer
MutSα, MutSβ	forms of MutS protein
MUTYH	MutY DNA glycosylase
NBS1	nibrin, a protein encoded by *NBN* gene
NEIL1	endonuclease VII-like 1
NEIL2	endonuclease VII-like 2
NER	nucleotide excision repair
NHEJ	non-homologous end joining
OvC	ovarian cancer
OGG1	gene encoding 8-oxoguanine glycosylase
p	phosphate
p8	transcriptional regulator p8
p34	protein kinase p34
p44	protein activator p44
p52	matrix protein p52
p53	tumor suppressor protein p53 encoded by *TP53* gene
p62	ubiquitin-binding protein p62
P-gp	P-glycoprotein 1 encoded by *MDR1* gene
PARP	Poly-ADP ribose polymerase
PARPis	Poly-ADP ribose polymerases inhibitors
PCNA	proliferating cell nuclear antigen, DNA clamp
PFI	platinum free interval

PI3K/Akt pathway	phosphatidylinositol-4,5-bisphosphate 3-kinase / AKT serine/threonine kinase pathway
PMS2	PMS1 homolog 2, MMR component
PNKP	polynucleotide kinase 3´phosphatase
pol β	DNA polymerase β
pol δ	DNA polymerase delta
pol ε	DNA polymerase epsilon
pol Θ	DNA polymerase theta
POLQ	gene encoding DNA polymerase theta
pRb	retinoblastoma protein encoded by *RB* gene
PTEN	phosphate and tensin homolog
RAD23B	RAD23B Homolog B, NER protein
RAD50	RAD50 double strand break repair protein
RAD51	RAD51 recombinase
RAD51C	gene encoding Rad51 paralog C
RAD51D	gene encoding Rad51 paralog D
RAD52	DNA repair protein RAD52
RFC	replication factor C
RNA	ribonucleic acid
RNAP II	RNA polymerase II
RPA	replication protein A, heterotrimer composed of RPA1, RPA2 and RPA3
SDSA	synthesis-dependent strand annealing
SLC transporter	solute carrier transporter
SNP	single nucleotide polymorphism
SSB	single strand break
ssDNA	single-stranded deoxyribonucleic acid
T	thymine
TCR	transcription coupled NER
TFIIH	transcription factor II human
TP53	gene encoding tumor suppressor protein p53
TSG	tumor suppressor gene
UV light	ultraviolet light
XPA	DNA repair protein complementing XP-A cells
XPB	TFIIH basal transcription factor complex helicase XPB subunit
XPC	xenoderma pigmentosum complementation group C, DNA damage recognition protein involvd in GGR
XPD	TFIIH basal transcription factor complex helicase XPD subunit
XPF	xeroderma pigmentosum complementation group F
XPG	DNA repair protein complementing XP-G cells
XRCC1	X-ray repair cross-complementing protein 1

1 Ovarian Cancer – a General Introduction

Ovarian cancer (OvC) is malignant neoplastic disease and the most common cause of death from gynecologic cancers, being the fifth leading cause of cancer death in women. The estimated incidence is 15.1 cases per 100 000 women in the Czech Republic (Ferlay *et al.*, 2013) and 6.1 cases per 100 000 women worldwide with nearly 239 000 new cases of OvC diagnosed in 2012 (Sundar *et al.*, 2015). The high mortality of the disease, accounting for almost 152 000 of deaths in 2012 (Ferlay *et al.*, 2015), is associated with the problems with early diagnosis and an initiation of treatment at advanced stages.

Ovarian carcinomas develop for long asymptomatically or with nonspecific symptoms, the lack of effective and sensitive biomarkers makes the early diagnosis difficult. On the other hand, early start of therapy increases the survival rate and could prevent the spread of cancer to lymphnodes and distant organs (metastases). At early-stage, when the cancer is localized only in the part of the body where it emerged, the 5-years survival among patients with OvC is aproximately 92,5 %. In more advanced stages, the 5-years survival rate decreases significantly to 73 % for stage II and III which means, that cancer already spread to surrounding tissue. For stage IV, when the cancer spreads to distant parts of the body, the 5-years survival is only 28,9 % (based on data covering a period 2007-2010) (https://seer.cancer.gov). In this late stage, the complete surgical removal of the tumor in combination with chemotherapy and subsequent recovery is already complicated.

1.1 Histological Features

OvC is a heterogeneous disease which can develope in the ovary´s epithelial, germ or stromal cells. Epithelial ovarian cancer (EOC) represents the predominant part (85 % to 90 %) of all OvCs and is classified in four major histological subtypes – serous cystadenocarcinoma (42 %), clear cell carcinoma (6 %), endometrioid carcinoma (15 %) and mucinous cystadenocarcinoma (12 %). Undifferentiated carcinoma accounts for 17 % of the disease (Di Saia & Craesman, 2012).

1.2 Genetic and Epigenetic Aspects

Family history of OvC and other gynecologic malignancies represents the strongest factor affecting a risk of developing OvC (Stratton *et al.*, 1998). However, only about 10 % of OvC cases are thought to be hereditary, while the remaning 90 % of diagnosed OvC cases are sporadic. Hereditary OvC risk is related to the family history of the disease. On the contrary sporadic cancer means the cancer arising from spontaneous (mainly somatic) mutations on the base of environment and life style interaction. Many high-penetrance susceptibility genes, such as *BRCA1* and *BRCA2* encoding breast cancer type 1 and 2 susceptibility protein (Rish, 2001), *MSH2* encoding mutS homolog 2, *MLH1* encoding mutL homolog 1, *MSH6* encoding mutS homolog 6 (Bondana *et al.*, 2011), and moderate-penetrance susceptibility genes, such as *RAD51C* and *RAD51D* encoding Rad51 paralog C

and D (Song *et al.*, 2015) and *BRIP1* encoding BRCA1 interacting protein C-terminal helicase 1 (Rafnar *et al.*, 2011) have been identified in hereditary forms of OvC. Low-penetrance genetic variants are believed to account for remaining excess of relative risk and often have no backround in family history of the disease.

Carrying a single-gene mutation may predispose to more than one cancer type. Women with germline mutations in *BRCA1* and *BRCA2* tumor suppressor genes, which account for about 9/10 hereditary OvC cases (Boyd, 2003), exhibit apart from the high risk of developing OvC also an increased risk of developing breast cancer (Miki *et al.*, 1994; Lancaster *et al*., 1996). This type of mutations is known as hereditary breast and ovarian cancer syndrome (HBOC). *BRCA1/2* are reponsible for the repair of DNA double strand breaks (DSBs) using homologous recombination and thus maintain genetic stability of the cell. Mutations in *BRCA1*, located on chromose 17q, and *BRCA2*, located on chromosome 13q, account for the most common cause of hereditary OvC. There is also a tight link between colorectal cancer (CRC) and certain extracolonic cancers such as OvC. Disorder predisposing to these cancer types arise from inherrited mismatch repair (MMR) deficiency and is known as Lynch Syndrome (LS) or hereditary nonpolyposis colorectal cancer (HNPCC). Having this condition makes patients unable to repair DNA replication errors, which lead to microsatellite instability (MSI) and subsequent malignant transformation. Individuals with LS have life time risk of developing CRC of about 80%, whereas women with LS have about an 8% life time risk of OvC (Vasen *et al.*, 1996). Even thought LS is genetically heterogenous and is confirmed by mutation in at least one of multiple MMR genes, both MMR-related OvC and CRC occur due to alterations in the same *MLH1*, *MSH2* or *MSH6* genes (Ketabi *et al.*, 2012; Barrow *et al.*, 2008).

Epigenetic changes in DNA repair genes play an important role in the onset of sporadic OvC either. These modifications often arise in response to outer or enviromental factors and significantly influence the way how the genes will be transcribed without altering the DNA sequence. Unlike the changes in DNA sequence, epigenetic modifications are frequently reversible and can serve as prospective target of epigenetic therapy (Heerboth *et al.*, 2014). Discovery of epigenetic alternations involved in gene transcription control (such as methylation) (Wei *et al.*, 2006) or in post-transcriptonal modifications (such as non-coding RNAs regulation) (Chung *et al.*, 2013) may further contribute to the development of new biomarkers, applicable both in diagnostics and in design of optimized therapeutical regimen. Epigenetic changes are specific for each of four OvC histological subtypes. The most common epigenetic deregulations linked to OvC are aberrant methylation (Catteau *et al.*, 1999), histone modifications (Caslini *et al.*, 2006) and expression of non-coding RNAs (Iorio *et al.*, 2007) regulating gene trancription. When dealing with inappropriate methylation, cytosine-phosphate-guanine (CpG) islands are frequently hypermethylated in OvC as well as in other cancers (Teodoridis *et al.*, 2005). CpG islands are typically located within gene promoters and their hypermethylation often mediates corresponding gene repression. On the other

hand, DNA hypomethylation event affects mostly non-coding DNA, particularly transposable elements and repeat sequences, and has also impact on OvC onset (Widschwendter *et al.*, 2004).

1.3 Risk Factors

The risk of developing OvC grows with increasing age, 45 % of all ovarian carcinoma occurs in postmenopausal women older than 65 years (based on data covering a period 2010 – 2014) (https://seer.cancer.gov). Recent studies show that the use of oral contraceptives can be protective against disease development. This protection becomes more efficient with duration of use (each 5 years of use decrease the risk of OvC by 20 %) and has been pronounced among *BRCA1/2* mutation careers (Cibula *et al.*, 2010). As one of the likely explanations seems the effect on number of ovulation cycles. During the ovulation, ovarian surface epithelium undergoes repeated mictrotraumas. Epithelium becomes liable to faulty DNA replication and thus the probability of cell tranformation into cancerous cell increases (Fathalla, 1971). From this reason, the lenght of menopause (Casagrande *et al.*, 1979), full-term pregnancy (Adami *et al.*, 1994) and breastfeeding (Chiaffarino *et al.*, 2005) might also lower the risk of OvC. Women who have been full-term pregnant have a reduced risk of OvC compared to women who have not given birth. This risk decreases with every single birth at full term. Besides, it has empirically been observed that gynecologic surgical procedures like hysterectomy and tubal ligation also have a benefical influence on OvC prevention (Hankinson *et al.*, 1993). The involvement of hormones in OvC etiopathogenesis is also significant. According to several theories, mitigation of gonadotrophin levels and estrogens along with elevated progesterone have an infuence on cancer risk reduction (Vanderhyden, 2005).

1.4 Treatment

A frequent problem related to the OvC treatment is developing drug resistance in patients who were initially resposive to chemotherapy. As terapeutic agents, paclitaxel and carboplatin are commonly used. Acquired resistance can result from an activation of energy dependent transport proteins (Samimi *et al.*, 2004), known as efflux pumps, that are after their overexpression able to detect and exclude the xenobiotics or their metabolites from the cell. Among these proteins, P-glycoprotein 1 (P-gp), ATP-binding cassette (ABC) transporter with broad specifity, is of importance (Bell *et al.*, 1985). Additionally, secondary somatic mutations in OvC relevant genes such as *BRCA1/2* (Norquist *et al.*, 2011) may undelie the onset of the resistence towards chemotherapeutics. Epigenetic therapy in combination with some chemoterapeutic agents poses an option in chemoterapeutic sensitivity restoration (Matei *et al.*, 2012). Apoptotic pathways activation is another treatment approach in OvC (Sasaki *et al.*, 2000). Due to the overexpression of some anti-apoptosis factors and executional caspases inhibition, fraction of the OvC cell become resistant to chemoterapeutics and subsequent therapy loses its efficiency. B-cell lymphoma 2 (BCL-2)

and tumor suppressor protein p53 (p53) family of apoptosis regulator proteins (Eliopoulos *et al.*, 1995) and phosphatidylinositol-4,5-bisphosphate 3-kinase / AKT serine/threonine kinase (PI3K/Akt) pathway (Lee *et al.*, 2004) are potential candidates for resistance adjustment.

2 What is DNA Repair and Why is Important; a) in General and b) in Relation to Ovarian Cancer Etiology

DNA repair is the biological process by which the cell recognizes and corrects damaged DNA. This mechanism is essential for the long life span of the cell and preventing error accumulation. In case that these repair processes fail and the cell does not undergo apoptosis or senescence, DNA lesions persist in the organism and may be transmitted from the one cell generation to the other. As a last resort, accumulated mutations contribute to carcinogenic process.

Seven major types of DNA repair pathways are implicated in DNA damage response (DDR). Arising DNA DSBs can be repaired by homologous recombination (HR), non-homologous end joining (NHEJ) or microhomology-mediated end joining (MMEJ). By contrast, single strand breaks (SSBs) are repaired by mechanisms including base excision repair (BER), nucleotide excision repair (NER) and mismatch repair. Direct reversal of DNA damage makes another possibility to fix DNA strands. SSBs arise in cells from attack of reactive oxygen species, intracellular metabolites, from the intrinsic DNA instability and also as DNA repair intermediates, whereas ionizing radiation, reactive free radicals and recombination across a nick predominantly account for formation of DSBs. Additionaly, some DSBs and SSBs are not formed directly, but as a consequence of the attempted repair by BER. This potential damage is associated with UV exposure, bulky lesions and platinated derivates. In context of OvC, four major types of DNA repair such as HR, NER, BER and MMR have been reported.

Faulty DNA repair pathways pose a risk especially if unrepaired DNA damage occurs in tumor supressor genes (TSGs) or proto-oncogenes. In both instances, it results in non-controlled cell proliferation. Loss of tumor suppresor functions and activation of proto-oncogene usually arise fom deletion, epigenetic silencing and mutation of germline or somatic origin. In epithelial OvC, somatic variants of mutation predominate notably over these with hereditary character. The prevalence of OvC cases arises from somatic alterations (in more than 90 %), whereas remaining less than 10 % of cases are associated with germline mutations (Narod *et al.*, 1994).

2.1 Tumor Suppressor Genes

Tumor suppressor genes are negative regulators, which coordinate cell division by stopping or slowing its proliferation during the mitotic phase G1. Mutations in tumor suppressor genes have

usually recesive character and can be hereditary as well as somatic origin. In the former case, one defective allele is inherited and the disease develops later by somatic inactivation of the second allele. In the latter case, the loss of both alleles happens throught somatic mutation. Major tumor suppressor genes associated with epithelial OvC encode BRCA1 (Miki *et al.*, 1994), BRCA2 (Lancaster *et al.*, 1996), p53 (Marks *et al.*, 1991), phosphate and tensin homolog (PTEN) (Saito *et al.*, 2000), caveolin 1 (CAV1) (Miotti *et al.*, 2005) and retinoblastoma protein (pRb) (Li *et al.*, 1991). All these genes are required for DDR – to find DNA lesion and throught the signalization promote its repair. Obviously, their defect leads to loss of control over the DNA damage.Cells with disabled tumor suppressor genes manifest sensitivity to DNA damaging agents as well as predisposition to disease development.

2.2 Proto-oncogenes

By contrast, proto-oncogenes stimulate the cell growth and governs its proliferation in each of the checkpoints. Through mutation, they change to oncogenes. Since the proto-oncogene is transformed into oncogene, it can not restrain cell division and cell can grow out of control. Fortunately, single mutated oncogene is still usually insufficient to start tumorigenesis assuming the proper function of tumor suppresor genes. Pivotal proto-oncogenes involved in ovarian cancer are v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) (Mok *et al.*, 1993), myc proto-oncogene protein (c-myc) (Baker *et al.*, 1990), AKT serine/threonine kinase 1 (AKT1), AKT serine/threonine kinase 2 (AKT2) (Altomare *et al.*, 2004) and human epidermal growth factor receptor 2 (HER-2/neu) (Berchuck *et al.*, 1990).

3 DNA Repair Pathways

3.1 Homologous Recombination Repair

Homologous recombination (HR) refers to several processes by which a cell exchange similar or identical DNA segments between the two strands. This mechanism occurs not only in meiotic prophase I to create genetic variation, but it is also applied in repairing DSBs, which are extremely harmful types of DNA lesions. The programmed formation of DSBs is induced mainly during meiosis, to carry out genetic exchange between homologous chromozomes. Common environmental damage, in which HR is employed, includes radiation (Corry & Cole, 1968), UV light (Covo *et al.*, 2012) and crosslinking agents (McHugh *et al.*, 2000). In this instance, DSBs arise indirectly as an intermediate after the cross-link removal.

3.1.1 Mechanism

Homologous recombination repair (HRR) (Fig. 1 on page 7) is initiated by MRN complex, a heterotrimeric protein consisting of double-strand break repair protein Mre11, DNA repair protein RAD50 and protein NBS1, which binds to DSB (de Jager *et al.*, 2001). Mre11 then catalyses the short-range resection of 5′ends at the break site (Paull & Gellert, 1998). Althought generated 3′ tails are usually sufficient to promote DSB reapir, either exonuclease 1 (EXO1) (Tran *et al.*, 2002) or RecQ helicases together with DNA2 helicase (Sturzenegger *et al.*, 2014) ordinarily continue processing these intermediates to produce a long overhanging 3′ tails. In this stage, replication protein A (RPA) binds to exposed single-stranded DNA (ssDNA) and prevents the formation of secondary structures (Pestryakov *et al.*, 2003), because ssDNA serves as a substrate for RAD51 protein (Ma *et al.,* 2016). RAD51 assembly is mediated primarily by BRCA2 (A. A. Davies et al., 2001), however in case of BRCA2 deficiency, RAD52 DNA repair protein (RAD52) may supply its function (Feng *et al.*, 2011). BRCA1 also interacts with RAD51 and its function seems to be similar to BRCA2 (Scully *et al.*, 1997). When RAD51 is loaded onto the ssDNA, it searchs for sequence homology and facilitates the pairing between 3′ssDNA overhang strand and undamaged homologous duplex (Baumann *et al.*, 1996). During homologous exchange, invading strands form a complex called displacement loop (D-loop), which consist of new heteroduplex and the displaced strand originating from former duplex. In the next step, new nucleotides are synthetized by polymerase from 3′ends and joined together with the second DSB ends. This intermediate is known as holliday junction (HJ). Resolution of the HJ by nicking two strands (Constantinou *et al.*, 2001) results in recombinant crossover or non-crossover double-stranded DNA (dsDNA) as a final product. Nevertheless, during mitosis the DSB repair product is most likely non-crossover and it is provided by synthesis-dependent strand annealing (SDSA) HR-mediated pathway (Stark & Jasin, 2003). On the contrary, during the meiosis another HR-mediated pathway called double strand break repair (DSBR) can lead either to crossover or non-crossover. The choice between these two options relies on the orientation of HJ cutting, especially since double holliday junction (DHJ) is formed in this repair model (Allers & Lichten, 2001). In SDSA, single HJ is the only intermediate.

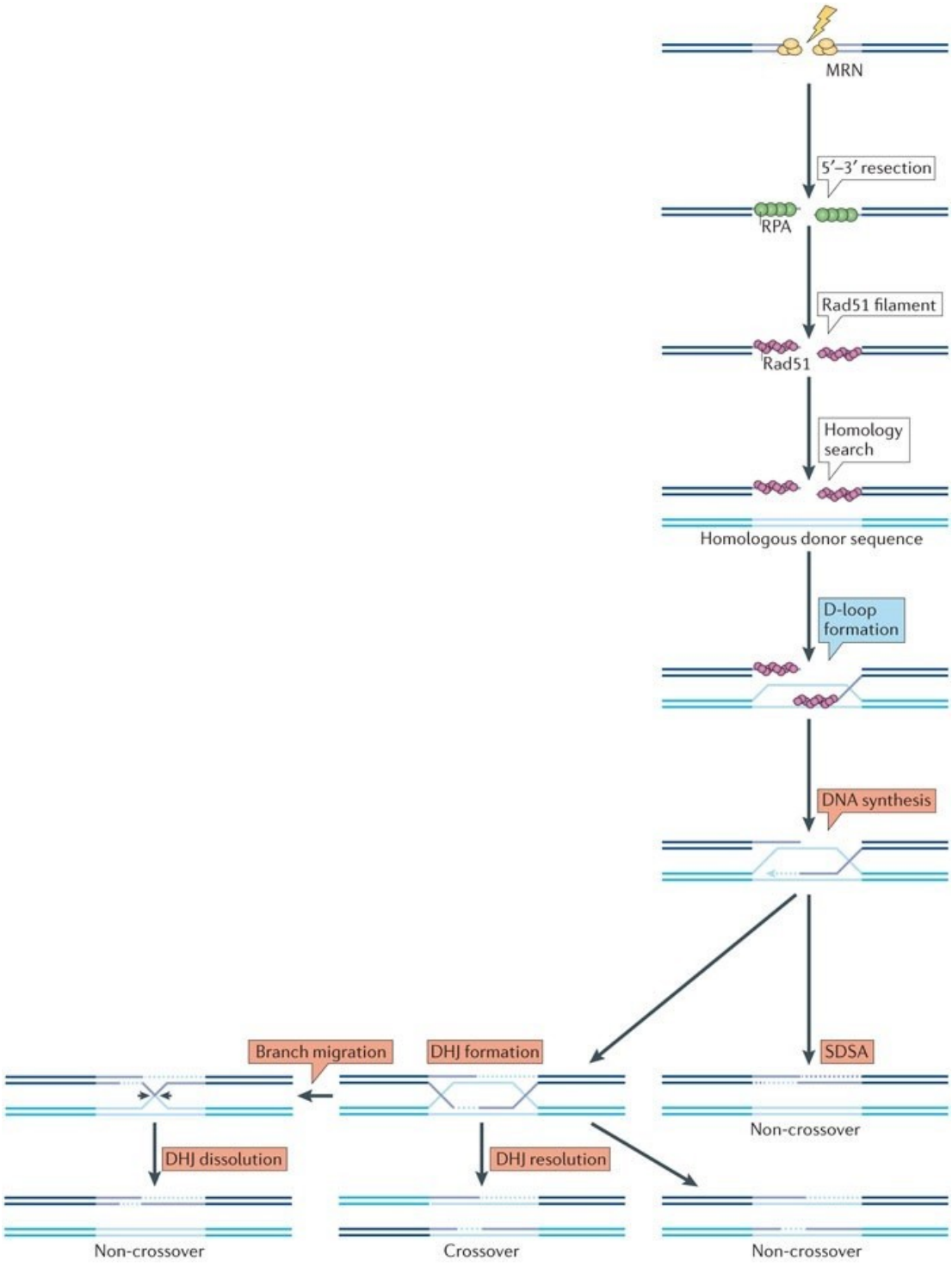

Fig. 1 **The homologous recombination repair.** General scheme of the SDSA and DSBR pathway (adapted from Renkawitz *et al.*, 2014)

3.1.2 Links between Homologous Recombinaton and Cancer

DNA repair by HR is essential for the accurate repair of DSBs. Thus, genetic elements or cellular events that turn off HRR result in high frequency of mutations within the genome and potential cancer development. Impaired HR is responsible for several cancer phenotypes,

especially ovarian and breast cancer. In OvC cell, HR deregulation is driven mostly by somatic and germline mutations in *BRCA1/2* (Moynahan, 1999; Moynahan et al., 2001). Less common defects occur in core *RAD* genes *RAD51* and *RAD52* (Tong *et al.*, 2003), *CDK12* (Ekumi *et al.*, 2015) and other HR DNA damage genes. *BRCA1* and *RAD51C* promoter methylations were also described in this connection (Baldwin *et al.*, 2000; Meindl *et al.,* 2010). When HRR aparratus fails, the cell still have two alternative DSBs repair pathways: NHEJ and MMEJ. Current studies indicate that NHEJ suppression occurs besides other things also in context with *BRCA1* mutation (Bau *et al.*, 2006). In contrast to *BRCA1*, *BRCA2* status have been demonstrated to affect only HRR (Xia *et al.*, 2001).

3.1.2.1 DNA Polymerase Theta and Its Role in Homologous Recombination Repair

DNA polymerase theta (pol Θ) upregulation is frequently reported in ovarian carcinoma. Pol Θ is a family A DNA polymerase involved in DSBs repair. It is an error-prone enzyme encoded in humans by the *POLQ* gene. Its very low fidelity comes from the lack of proofreading activity and error rate, which is more than 10-fold higher than for other two human proofreading-deficient A family polymerases (Arana *et al.*, 2008). Human pol Θ has moderate processivity and synthesizes chains that differ in length from 1 to more than ~75 nucleotides (Arana *et al.*, 2008). Pol Θ has highly conserved structure among multicellular organisms and it is made up of four subunits. N-terminus forms a helicase-like domain, comprising several structural motifs characteristic for DNA and RNA helicases. The central domain contains RAD51 interacting motif, while C-terminal domain serves as the polymerase activity hub. It was proved that the expression of pol Θ inversely correlates with expression HR genes and inhibits HRR pathway (Ceccaldi *et al.*, 2015). This inhibition is realized by pol Θ ability to bind RAD51 recombinase, thus pol Θ prevents the RAD51 assembly on ssDNA binding proteins and blocks RAD51-mediated HR. On the basis of cell´s ability to carry out HR, different situations may occur. In the first case, lowering the pol Θ expression in HR-proficient cells has the consequence in HR activity upregulation. While in the cancer cells defective in HR and incapable of pol Θ production, the loss of pol Θ increases cell death. HR-deficient cells with upregulated pol Θ expression are observed in various cancers, most frequently in ovarian and hereditary breast cancer. It was found out that in epithelial ovarian cancers, pol Θ expression has upward trend depending on tumour grade (Ceccaldi *et al.*, 2015).
From the studies mentioned above it may be deduced that by reducing the pol Θ synthesis, cancer cells become more sensitive to anti-cancer drugs and radiation. This finding could therefore have a potential use for new cancer therapy targeting at pol Θ knockdown. According to these results, pol Θ seems to be also a prospective biomarker in cancer prognosis.

3.1.2.2 Association of Human RAD51 Protein with Ovarian Cancer Risk

Human RAD51 protein is also connected with OvC risk. The main importance of RAD51 is providing DNA pairing and strand exchange. RAD51 protein family is known to be cooperating

with BRCA2. Their interaction appears to be crucial mainly because of the fact that after initial end resection step of HRR, BRCA2 promotes RAD51 targeting to newly emerged 3´tailed DNA and its assembly on it. Under normal conditions, BRCA2 binds RAD51 with about six RAD51 molecules per one of BRCA2, where the number of RAD51 bound grows up linearly with its concentration and is dependent on content of BRC repeats in BRCA2. With regard to DNA binding affinity of BRCA2, ssDNA substrate, especially tailed ssDNA generated on DNA duplex, is strongly preferred as compared to dsDNA. Thus the presence of BRCA2 is also required for prevention of RAD51 binding to dsDNA (Jensen *et al.*, 2010). Among other things, BRCA2 maintains DNA strand exchange in a concentration dependent manner using ATP for energy. During its loading onto ssDNA, RAD51 competes for the same binding sites with RPA and displaces it due to its tight bonds with DNA very slowly. RPA makes complex with ssDNA and keeps DNA strands unwound for replication, initial phase of HR or nucleotide excision repair process. Increasing amount of BRCA2 supresses the inhibition caused by RPA and stimulates DNA strand exchange (Jensen *et al.*, 2010).

RAD51 protein family also fix DNA crosslinks induced by various reactive groups or radiation agents. Two kinds of these lesions can arise. Intrastrand crosslinks occur by covalent connection between bases in the same DNA strands, while interstrand crosslinks (ICLs) occur between residues in the opposite strands. DNA modified in this way poses a serious threat because crosslinking of DNA forms an obstacle to the separation of complementary strands. Thereby DNA replication and transcription is potently inhibited. RAD51 paralogs form an BCDX2 complex, which is implicated along with HELQ helicase (HELQ) in ICL repair pathway. Another complex made up of RAD51 paralogs, CX3 complex, does not tightly participate. HELQ performs its role by unwinding DNA strands at blocked replication fork and acts directly with BCDX2. Because of this fact, HELQ and BCDX2 show themselves as the indispensable elements of the whole HRR process and affect sesitivity to ICLs. Experiments have demonstrated that humans with deficiency of HELQ are predisposed to ovarian and pituitary tumorigeneses. Fertility deffects linked to smaller genitalia and germ cell depletion and more frequent tendency to form ICL have been reported as well (Adelman *et al.*, 2013). All in all, individuals with HELQ deficiency have the similar phenotype like these with Fanconi anemia (FA) disease. Following experiments authenticate that both pathways are mutually independent, where HELQ corresponds to Fanconi anemia complementation group D 2 protein (FANCD2) in FA pathway (Adelman *et al.*, 2013). Cells with silenced HELQ genes seem to be sensitive to cisplatin and mitomycin C (MMC), other tested DNA-damaging agents are not effective permanently (Takata *et al.*, 2013). With regard to all these facts mentioned above, *HELQ* gene may be potential genetic marker for OvC diagnosis.

3.2 Mismatch Repair

DNA mismatch repair is a system that ensure error recognition and correction processes during DNA replication and recombination. During DNA replication, it maintains removal and fixing erroneously incorporated bases, that have escaped DNA polymerase proofreading, using parental strand as a template. The same MMR machinery proceeds mismatched nucleotids in heteroduplex formed during homologous recombination. In contrast, gene conversion between divergent sequences is intesively inhibited by MRR proteins.

3.2.1 Mechanism

The human MMR system (Fig. 2 on page 11) is ensured by the Mut proteins, namely by methyl-directed mismatch repair proteins MutS (MutS) and MutL (MutL) homologous to the bacteria Mut proteins. MutS is a heterodimeric ATPase constituted of MSH2/MSH6 (MutSα) or MSH2/MutS homolog 3 (MSH3) (MutSβ) subunits (Obmolova *et al.*, 2000), just as MutL constituted of MLH1/PMS1 homolog 2 (PMS2) (forming MutLα), MLH1/PMS1 (forming MutLβ) or MLH1/Mutl homolog 3 (MLH3) (forming MutLγ) (Kadyrov *et al.*, 2006; Räschle *et al.*, 1999; Cannavo *et al.*, 2005). The initial step of base-base mistmach recognition is provided by MutS, which binds to DNA near the mismatch site (Tessmer *et al.*, 2008) and from afar comunicates with methyl-directed mismatch repair MutH (MutH). Meanwhile, MutH searches hemimethylated dGATC sites in daughter DNA and when identifies such site, it induces DNA bending (Längle-Rouault *et al.*, 1987). The task of another MMR protein MutL is to coodinate individual MMR components (Ban & Yang, 1998). First of all, MutL joins the MutS-DNA complex and via MutS mediates MutH activation. This event allows MutH to generate nick near the hemimethylated site. At the same time, one of the ssDNA endonucleases, depending on the break position relative to the mistmach, is activated by MutS (Genschel & Modrich, 2003) and degrades arising DNA strand as it becomes unwound. In the distance of about 100 bp beyond the mismatch, MutL terminates endonuclease activity and nascent ssDNA is rapidly occupied by SSB proteins, which prevent formation of DNA secondary structure as well as protect ssDNA from being cleaved by endonuclease. In the presence of the prolifrating cell nuclear antigen (PCNA) DNA clamp and replication factor C (RFC), DNA polymerase delta (pol δ) then adds new bases until the gap is completely filled. Ultimately, DNA ligase 1 (LIG1) is employed to seal the nick and MMR is completed (Zhang *et al.*, 2005).

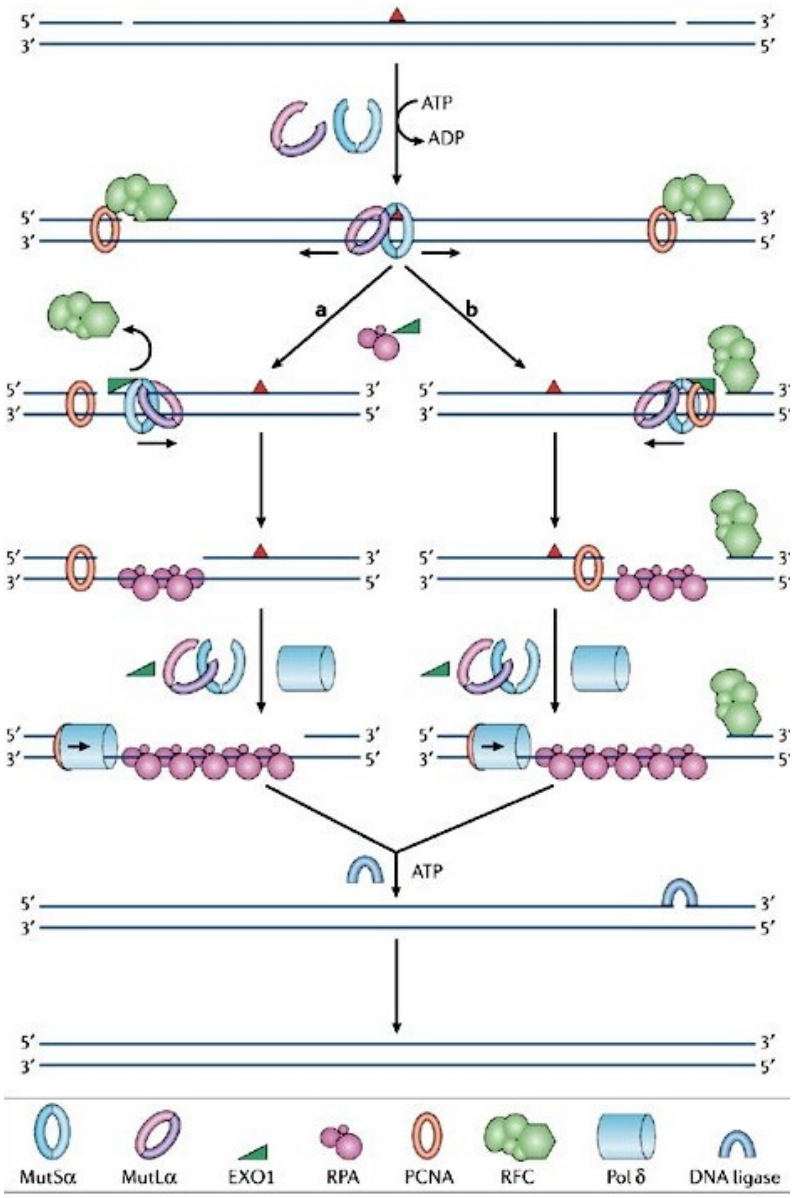

Fig. 2 **The mismatch repair.** General scheme (adapted from Jiricny, 2006)

3.2.2 Links between Mismatch Repair and Cancer

Defect of any kind of Mut proteins may result in microsatellite instability (MSI), pathogenic gene conversion and in the worst case also multistep tumorigenesis (Xue *et al.*, 2014). Microsatellites are fragments of repetitive DNA (mainly adenine (A) or adenine-thymine (AT)), they come into existence by replication slippage while the daughter strand of DNA is forming. Replication slippage often occurs in tandem repeat sequences which involves DNA polymerase to separate from the template. As follows, incomplete daughter strand strand slips out from it and pairs with another direct repeat in the 3´to 5´direction. DNA polymerase then reattaches to the daughter strand upstream and continues to copy the template. However, as a consequence of the new strand pairing, DNA loop on one of the strands is generated. If the loop is formed on daughter strand, extra nucleotides are

incorporated becuse DNA polymerase inserts the same nucleotides already added before. If the template loops out, DNA polymerase skips over one or more nucletides and the deletion is introduced. These incorrect sequences can be fixed easily if operated under normal circumstances. However, impaired MMR can not cope with these errors, which often results in frame-shift mutations. When a frame-shift occurs in cancer-related genes, it can induce loss of their function that ultimately leads to cancer.

MMR deficiency is the whole phenotype in CRC and its hereditary form, LS (HNPCC), is crystallical example. This is also the reason why deficiencies in MMR predispose patients to get as a second cancer OvC (in case of CRC) or CRC in OvC patients. MMR deficiency affects OvC etiology from about 10% to 15% (Bewtra *et al.*, 1992).

MMR disfunction may have both genetic and epigenetic origin. Mutations in DNA MMR genes account for the most cases of hereditary OvC excluding *BRCA1* and *BRCA2* gene defects. Inherited MMR deficiency is frequently associated with LS, formerly known as HNPCC. LS is an autosomal dominant genetic condition caused by defective MMR proteins, mostly by *MSH2* and *MLH1* (Dowty *et al.*, 2013). Patients with LS face high predispositions to CRC and also increased likelihood of developing endometrial, ovarian, stomach, small intestine and numerous diffeent types of cancer (Watson *et al.*, 2008). LS-associated ovarian cancer subtypes are very variable, mixed endometrioid/clear cell type prevails. Mutations in *MSH2* affect 47 % and in *MLH1* 38 % of women (Helder-Woolderink *et al.*, 2016). Simultaneous mutation on both *BRCA1/2* and MMR genes is a rare event. In this context, co-occurrence of *BRCA1* and *MSH6* truncation mutations was reported in patients with endometrial cancer (EC) (Kast *et al.*, 2012).

At present, genetic MMR disorders such as Lynch-like syndrome (LLS), sporadic MSI CRC cancer and constitutional MMR deficiency (CMMRD) also come under the umbrella of HNPCC. Patients with LLS have seemingly the same symptoms as those with LS. They manifest high MSI and lack MMR proteins. Unlike them, however, LLS patients do not exhibit germline mutations or methylations in MMR genes (Rodríguez-Soler *et al.*, 2013). Exact mechanism of MMR inactivation is still under investigation.

As for other mentioned disorders, sporadic MSI CRC makes about 15 % of all sporadic CRC cases (Hampel *et al.*, 2005). It stems mostly from a biallelic hypermethylation of *MLH1* promoter, *BRAF*(V600E) proto-oncogene mutation is a common accompanying phenomenon (Vilkin *et al.*, 2009). The last-named CMMRD is highly penetrant syndrome which occurs rarely due to biallelic germline mutations in MMR genes (Bakry *et al.*, 2014).

Distinguishing between the particular MMR disorders is important because of their different familiar predispositions and colorectal and associated extracolonic cancers incidence. Increased personal chance of getting second primary cancer, such as OvC, applies to all HNPCCs.

3.3 Nucleotide Excision Repair

Nucleotide excision repair identifies and removes DNA helix-distorting lesions on ssDNA. In contrast to BER, NER recognizes general damage to DNA, such as bulky DNA adducts. Chemicals that form these alternations are mostly of exogenous origin and include especially products of oxidative metabolism (Reardon *et al.*, 1997) and many food carcinogens, such as polycyclic aromatic hydrocarbons (Braithwaite *et al.*, 1998), heterocyclic aromatic amines (Reeves *et al.*, 2011), heterocyclic amines (Felton *et al.*, 2007) etc.. From physical agents, UV radiation (Muñoz *et al.*, 2017) should not be forgotten.

3.3.1 Mechanism

NER (Fig. 3 on page 14) can be divided into two general subpathways: transcription coupled NER (TCR) (Mellon *et al.*, 1987), removing the lesions created on primary transcript during the gene transcription, and global genomic NER (GGR) (Yu *et al.*, 2016), removing the lesions occuring in the entire genome including the non-transcribed genes on DNA strand currently undergoing transcription. Both of the subpathways share the same repair mechanism but differ in early damage recognition step. In GGR, xenoderma pigmentosum complementation group C (XPC) complexing with RAD23B homolog B (RAD23B) and heterodimer consisting of DNA damage-binding protein 1 and 2 (DDB1/2) are required for recognising DNA damage. XPC/RAD23B is responsible for recognising distorting lesions (Kusumoto *et al.*, 2001) whereas DDB1/2 identifies damage caused by UV light (Wakasugi *et al.*, 2002). As for TCR, a DNA lesion stops replication fork and damage is recognized directly by RNA polymerase II (RNAP II) cooperating with Cockayne syndrome A (CSA) and B (CSB) proteins. Proper GGR function is tightly linked to *TP53* tumor-suppressor gene encoding p53 protein. If the p53 is not produced, GGR is interrupted. The following studies also reported that BRCA1 promotes GGR capacity independently on p53, when activates *XPC*, *DDB2* and *GADD45* gene expressions required for NER (Hartman & Ford, 2002). In TCR, BRCA1 involvement remains inconclusive.

The second step in NER process is damage verification. It is maintained by transcription factor II human (TFIIH), large multisubunit protein composed of ten subunits - TFIIH basal transcription factor complex helicase XPD subunit (XPD) (Shaeffer *et al.*, 1994) and TFIIH basal transcription factor complex helicase XPB subunit (XPB) (Hwang *et al.*, 1996), CDK-activating kinase complex (CAK) (Shiekhattar *et al.*, 1995) and several proteins including transcriptional regulator p8 (p8), protein kinase p34 (p34), protein activator p44 (p44), matrix protein p52 (p52) and ubiquitin-binding protein p62 (p62) (Bedez *et al.*, 2013). XPD and XPB unwind DNA and all the complex stops in damaged site (Evans *et al.*, 1997). When the presence of the lesion is confirmed, DNA repair protein complementing XP-G cells (XPG), which have the 3´-endonuclease activity (O´Donovan *et al.*, 1994) or excision repair cross-complementation group 1- xeroderma pigmentosum

complementation group F (ERCC1-XPF) enzyme complex, which have the 5′-endonuclease activity (Sijbers *et al.*, 1996), join the TFIIH. In addition, RPA and DNA repair protein complementing XP-A cells (XPA) repair proteins (Vasquez *et al.*, 2002) attach TFIIH and promote its interaction with DNA. In this point, preincision complex, which assembly is provided by XPD-DNA interaction (Vashisht *et al.*, 2015), is formed and endonuclease cleaves damaged DNA fragment. Resulting gap is filled by pol δ or by polymerase epsilon (pol ε), copying the undamaged DNA strand, in cooperation with PCNA, RFC and RPA – the same protein machinery required for DNA replication synthesis (Shivji *et al.*, 1995; Overmeer *et al.*, 2010). In the last stage of NER process, DNA nick is sealed either by LIG3-ERCC1 complex (Kusumoto *et al.*, 2001) or by LIG1, which exclusively serves in TCR (Levin *et al.*, 1997).

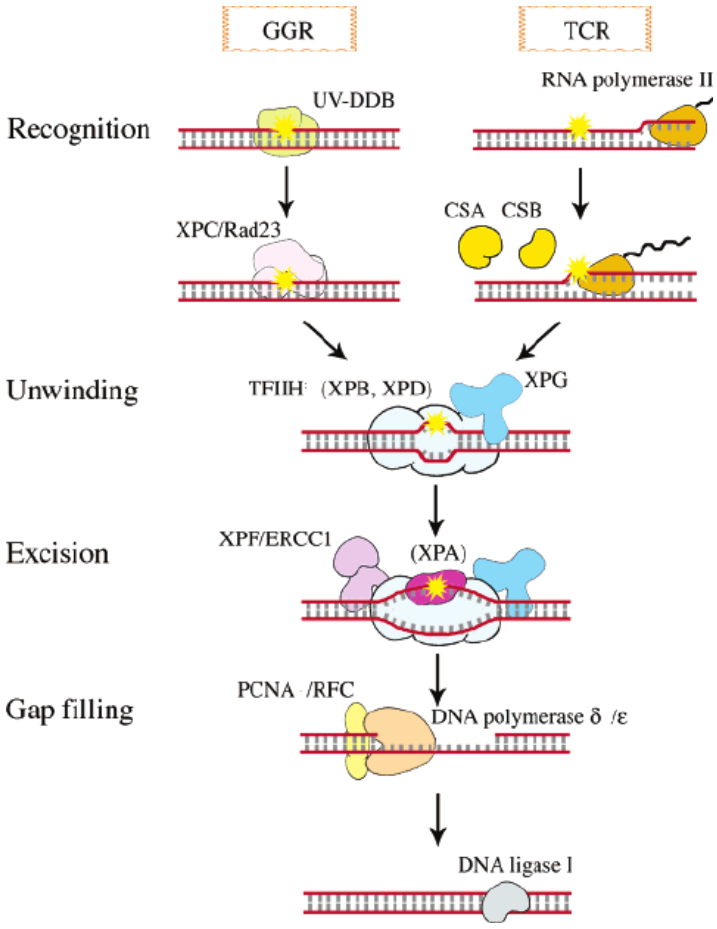

Fig. 3 **Nucleotide excision repair.** General scheme (adapted from Kimura & Sakaguchi, 2006)

3.3.2 Links between Nucleotide Excision Repair and Cancer

Under physiological conditions, NER is essential to protect the cell against the mutagenesis and beginning of carcinogenesis (an iniciation phase). Conversely, in some kind of cancer treatment

such as chemotherapy, loss of nucleotide excision repair capacity is even desired. It is because chemoterapeutics, such as overwhelming majority of alkylating and platinum-based agents, introduce bulky DNA lesion causing replication arrest and subsequent apoptosis, if NER apparatus fails. Hovewer, repair of DNA damage induced by methylating agents is almost always reliant on BER (Fishel *et al.*, 2007).

A textbook example of OvC treatmant that cause DNA damage is widely used cisplatin, cross-linking agent with chemical formula *cis*-$[PtCl_2(NH_3)_2]$. When getting inside the cell, one of its chlorides is displaced by water molecule. By this way, cisplatin converts into its active form and becomes more electrophilic. Bases on DNA strand, typically guanine, binds to the complex, because nitrogen-7 position of guanine is a strong nucleophile and can be easily attacked by cisplatin.and causes its dehydratation. Nitrogen-7 of adenine and also nitrogen-3 of cytosine less commonly bind to cisplatin, but they are not too reactive toward it. When the bond between the base and cisplatin is formed, remaining chloride of cisplatin is then displaced usually by another guanine and DNA crosslink is established. Intrastrand cross-links constitutes 90 % of all crosslinks and are formed between two adjacent bases (1,2-d(GpG) or 1,2-d(ApG)), remaining cross-links are interstrand (1,2-d(GpC)) or intranstrand between the purines separated by another base (1,3-d(GpNpG)). Impact of these harmful lesions depends mainly on NER, because it is responsible for their removal. As follows, NER is replaced by HRR which is applied to fix DSBs repair intermediate left by exonuclease or endonuclease activity within NER.

Partly due to enhanced NER (besides the activity of ABC and solute carrier (SLC) membrane transporters etc.), rapid development of drug resistance often occurs and complicates the effect of chemotherapy treatment. An interesting solution for dealing with this problem is a suppresion of NER making OvC cells to be more sensitive to DNA damage agents.

Undobtedly the most frequently mentioned NER protein when speaking of platinum resistance in OvC is ERCC1. This protein is required for NER, ICL repair and DSBs repair. Its increased expression is verifiably linked to more efficient NER and correlates with reduced sensitivity to cisplatin. Subsequent research confirmed that targeting of ERCC1 by antisence RNA improves the effectiveness of chemotherapy and suppresses NER activity (Ferry *et al.*, 2000; Selvakumaran *et al.*, 2003). Moreover, level of its expression can be useful for predicting platinum-based chemotherapy resistance.

3.4 Base Excision Repair

Base excision repair ensures removing specific small lesion from ssDNA and protects DNA from endogenous and exogenous small molecular mutagens. Such DNA lesions do not usually distort helix structure and are caused mainly by alkylation (Lau *et al.*, 1998), oxidation (Rusyn *et al.*, 2004), deamination (Cortellino *et al.*, 2011) and uracil misincorporation (Nilsen *et al.*, 2002).

3.4.1 Mechanism

Eleven damage-specific DNA glycosylases play a key role in human BER (Fig. 4 on page 17) process. This family of enzymes cleaves modified or misincorporated bases from DNA leaving apurinic/apyrimidinic (AP) sites in DNA structure (Jacobs & Schär, 2012). Some glycosylases such as endonucleases VII-like 1 (NEIL1) and 2 (NEIL2) have also lyase activity and in the next step cleave DNA backbone and remove 3′-α,β-unsatured aldehyde group. Phosphate retained at the 3′ terminus is then removed by polynucleotide kinase 3′phosphatase (PNKP) (Wiederhold *et al.*, 2004), in order to expose 3′OH group. On the other hand, monofunctional glycosylase are not able to form SSB and this task including all 3′ blocking groups removal have to be fulfilled by AP endonuclease 1 (APE1), which have also the diesterase activity (Suh *et al.*, 1997). Although the 3′OH terminus is free, at the 5′ terminus remaining deoxyribophosphate (dRP) has to be cut out by DNA polymerase β (pol β) (Matsumoto & Kim, 1995). Exposed 3′OH group enables polymerase to fill the gap by newly synthesized nucleotide and the repair is completed with nick sealing catalysed by DNA ligase 3 (LIG3) in complex with the X-ray repair cross-complementing protein 1 (XRCC1) (Abdou *et al.*, 2015). According to the number of removed nucleotides and also according to oxidation state of abasic sugar, nucleotide synthesis is processed either by short-patch BER (described above) or long-patch BER (Sattler *et al.*, 2003). If only one nucleotide is needed, short-patch BER is favoured, whereas synthesis of two up to ten nucleotides is within long-patch BER. Furthermore, pol β is only polymerase implicated in short-patch BER (Singhal & Wilson, 1993), whereas in long-patch BER besides pol β (Dianov *et al.*, 1999) there are also pol δ and pol ε involved (Stucki *et al.*, 1998). Pol β lacks the ability to cut oxidized or reduced 5′sugars out and that is the reason, why in such cases long-patch BER si preferred to short-patch BER. In long-patch BER, pol β, δ or ε, in presence of PCNA and RFC, displace modified sugar and form the 5′ flap intermediate, which is then resolved by flap endonuclease 1 (FEN-1) (Klungland & Lindhal, 1997) and sealed by DNA LIG1 (Sleeth *et al.*, 2004).

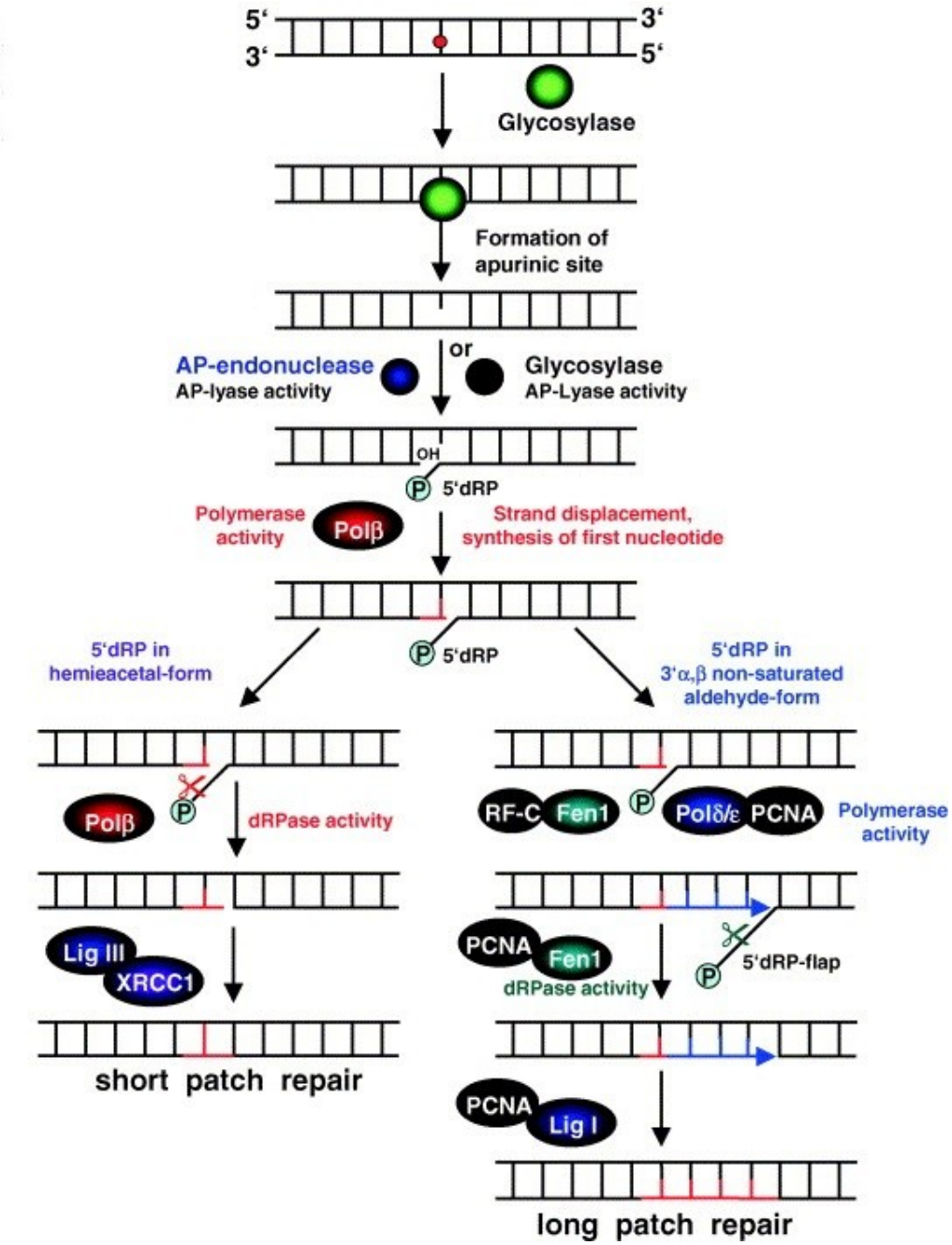

Fig. 4 **Base excision repair.** General scheme (adapted from Christmann *et al.*, 2003)

3.4.2 Links between Base Excision Repair and Cancer

DNA repair deregulation, including BER, leads to genome instability and often results in genetic diseases or oncogenesis initiation. Upregulation of pol β appears to be frequently reported in connection with human cancers including OvC (Bergoglio *et al.*, 2001), e.g. in *KRAS*(G12C)-mutated OvC cells (Caiola *et al.*, 2015). These data also suggest that pol β activity may support achieving drug resistance phenotype via enhanced NER.

Variants in MutY DNA glycosylase (MUTYH), recquired for excising oxidative DNA damage, cause MUTYH-associated polyposis (MAP). This autosomal recessive syndrome is chiefly attributable to an increased risk of CRC (Win *et al.*, 2014) and moderately also to an OvC risk (Vogt *et al.*, 2009). Regarding OvC, low expression of the *MBD4* gene, encoding methyl-CpG-binding domain protein 4 (MBD4), stemmed from its promoter methylation, was described in OvC and CRC (Howard *et al.*, 2009). MBD4 is DNA glycosylase, which targets spontaneously deamined bases and also binds by methyl-CpG binding domain to methylated DNA. Its downregulation results in MSI, decreased programmed cell death and mutations occuring more frequently in CpG islands.

Several single nucleotide polymorphisms (SNPs) were also found in *OGG1* and *APEX* genes in ovarian and endometrial tumors (Pieretti *et al.*, 2001). OGG1 encodes 8-oxoguanine glycosylase removing 8-oxoguanine DNA damage caused by oxidative stress. *APEX* encodes APE1 important in the process of single 5´DNA cleavage. However, somatic mutations in these genes were not identified. SNPs located in genes responsible for maintaining BER seem to be associated with genetic carriers of *BRCA1* and *BRCA2* mutations. The strongest relationship proved to exist between SNP rs1466785 in the *NEIL2* gene and *BRCA2* associated breast cancer risk, and between SNP rs2304277 in the *OGG1* gene and *BRCA1* associated ovarian cancer risk (Osorio *et al.*, 2014).

Targeting the cellular DNA repair system in order to improve the chemotherapy treatment is a common tool to fight cancer.To enhance the effect of alkylating agents using in OvC chemotherapy, BER regulation via one of the BER components, N-methylpurine DNA glycosylase (MPG), can be performed (Fishel *et al.*, 2007). This enzyme catalyzes the cleavage of alkylated and deaminated bases. A way to make the cell to be more sensitive to these types of lesions is to disrupt MPG repair mechanism by addition of some syntetic inhibitor such methoxyamine. This small molecule irreversibly inserts into a DNA-AP sites generated by MPG and prevents BER to be completed. Formation of such blocked AP sites leads to consequently increased presence of SSBs and DSBs and ultimate apoptosis.

Another approach to affect *BRCA1/2*-defective or in another manner HR-defective OvC cells is poly-ADP ribose polymerase (PARP) inactivation. This BER protein repairs SSB. When it fails, discontinuous DNA strands persist in the cell and during the replication, the DSBs can be easily formed. In normal cells, repair of DSBs is operated via HR. However in *BRCA1/2*-deficient cells, HR function is interrupted and its impairement is critical for cells survival (Ledermann *et al.*, 2016).

4 DNA Repair and its Role in Ovarian Cancer Therapy

There is a variability of treatment regimens. The medical procedure is reccomended according to stage of the disease and the cancer subtype. Advanced OvC is most successfully treated by surgery with subsequent chemotherapy (Griffiths *et al.*, 1979). Other options including hormone (Yokoyama & Mizunuma, 2013), radiation (Martinez *et al.*, 1985) or targeted therapy (Yap *et al.*, 2009) are used

as well. Therapy strategies that take into account particular cancer-critical genes make another interesting method of treatment.

Nevertheless, despite the initial good response to treatment, high percentage of patients experience cancer recurrence within two years from the start of the therapy. Cancer relapse depends on a variety of reasons such as tumor staging and grading, and the presence of remaining malignant tissue after debulking surgery (Rubin *et al.*, 1991).

4.1 Chemotherapy

Chemotherapy for OvC is often based on a combination of two or more drugs. Response to the first-line therapy is usually very high, but the cells quickly acquire a chemoresistance. Platinum compounds, including carboplatin or cisplatin, combined with taxanes, such as paclitaxel and docetaxel, prove to be similarly efficient in first-line therapy (du Bois *et al.*, 2003; Vasey *et al.*, 2004). However, carboplatin together with paclitaxel or docetaxel is mildly preferred because of the lower toxicity and better tolerability compared to cisplatin. These findings make platinum based chemotherapy a cornerstone of OvC treatment.

If the first line-therapy is not efficient, second-line therapy is initiated. Second-line treatment is chosen in agreement with molecular basis of particular chemoresistance and also with regard to length of platinum-free interval (PFI) (Markman *et al.*, 1991), which is defined as the time span between the completion of first-line therapy and the detection of relapse. Another criteria deemed important are drug toxicity and overall impact of treatment on health-related quality of life (Chase & Wenzel, 2011). According to PFI duration, patients can be separated into four categories as follows: a) platinum refractory (with disease progressing during the last line therapy or within four weeks after the end of the therapy), b) platinum resistant (with disease progressing between one and six months), c) potentially platinum sensitive (with disease progressing between six months and one year) and d) platinum sensitive (with disease progressing later than one year). Even though resistance to platinum changes over time, the response rate in second round is usually lower than that in initial chemotherapy. Platinum refractory or platinum resistant tumors are mostly treated by non-platinum drugs, namely by bevacizumab (Cannistra *et al.*, 2007), liposomal doxorubicin (Muggia *et al.*, 1997), gemcitabine (Friedlander *et al.*, 1998), topotecan (Creemers *et al.*, 1996) etc., whereas potentially platinum sensitive and platinum sensitive malignancies are ussually anew expose to platinum. Singleplatinum agents such as carboplatin are often used (Bolis *et al.*, 2001).

4.2 Hormone Therapy

OvC cells often contain elevated level of hormone receptors. Because of that, exposure to estrogens may promote their growth and proliferation, whereas progesterone and syntetic progestins have the exact opposite effect. Drugs able to block hormone receptors represent another possibility

to fight cancer. Good clinical results were achieved by treating with tamoxifen medication which binds competitively to the estrogen receptors (Karagol, 2007). It can however induce DNA adducts which are undesirable (Schild *et al.*, 2003). Inhibitors targeting aromatase, which participates in estrogen synthesis, were also proved to be helpful in ovarian cancer treatment (Smyth *et al.*, 2007). Nevertheless, hormone therapy serves mainly as additional treatment and its effect is not very significant.

4.3 Radiathion Therapy

OvC radiotherapy is currently rare and in the most cases serves as complementary treatment in selected spots, where the cancer appears (Dembo, 1992). OvC cells with *BRCA1/2* mutation evince hight sensitivity to ionizing radiation (Yuan *et al.*, 1999) and are suitable for radiation therapy regime.

4.4 Targeted Therapy

Targeted therapy represents modern approach selectively affecting cancerous cells with minimal impact to healthy cells. Drugs used in this type of therapy are mostly designed to focus on cell mechanisms different from their physiological state. The usual way of providing targeted therapy is switching of chemical signalization to cell division (Cao *et al.*, 2006), stopping intensified angiogenesis essential for cell nutrition (Spannuth *et al.*, 2008), blocking repair pathway leading to apoptosis (Helleday *et al.*, 2008) or blocking gene expression, e.g. by histone deacetylase inhibitors (Qian *et al.*, 2006). Histone deacetylases remove acetyl groups from the lysine ε-amino groups on a histone, thereby change the possitive charge of the histone to negative and enable DNA to be more accessible to transcription factors. Last but not least, imune system (Preston *et al.*, 2011) or toxin transport to cancerous cell (Shapira & Benhar, 2010) are currently exploited. Great sensitivity compared to high chemoterapeutic cytotoxicity and terapeutic effect only in desired site makes targeted therapy very attractive for future medical treatment. In this review, DNA repair and its regulation has been analysed in detail. Anticancer therapy focus on DNA repair pathways particulary due to the fact that enable cells to survive DNA lesions induced by chemotherapeutics. For that reason, inhibition of specific DNA repair pathways contributes to better response to chemotherapy and other therapies relied on induction of DNA damage. Currently used therapies evoke DNA damage e.g. by disruption in nucleotide metabolism (Aird *et al.*, 2014), polymerase inhibition (Ledermann *et al.*, 2012), inhibition of DNA damage sensors (Huntoon *et al.*, 2013) etc. Furthemore, some deficiencies induced in DNA repair pathways lead to their malfunction and the cell is forced to use alternative repair pathway (if available) (Fong *et al.*, 2010). The problem lies in compromised DNA repair ability in some cancer types. If the cancer cells have such alternative pathways impaired, it implicates accumulation of cytotoxic lesions, which can not be removed, and leads mostly to apoptosis.

5 Conclusion

This thesis summed up the most apparent molecular alternations observed in OvC tumors, which often elicit a reduced ability to repair DNA damage and deregulation of cell growth. The involment of the DNA repair pathways in cancer treatment have also been discussed. Since the DNA repair machinery is well-known, insight into its function allows therapies targeting the components of a particular repair pathway. DNA repair manipulation has a great potential, because throught its modulation, pro-apoptotic effect of chemotherapeutic agents can be enhanced.

DNA repair genes reported in the context of OvC may help with cancer diagnosis and detrmination of genetic predisposition to the disease. Many cancer screening test are currently used to detect cancer or are under development. Furthermore, understanding the impact of gene mutations/variants is essential to cancer prognosis.

Althought the OvC is extensively studied, its heterogenity and broad range of origin make the treatment difficult. For that reason, cancer therapy tailored to the particular genetic bacground of the disease offers new hope. However, further research is still needed to be knowledgeable in all physiological aspects and health hazards of the disease. It will particularly be dedicated to:

1) Proteomics and regulation of candidate DNA repair genes with function in OvC
2) Functional aspects of DNA repair system in OvC
3) Mechanistic studies of DNA repair function in OvC cells.

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