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Cell cycle regulation of human DNA repair and chromatin remodeling genes

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ABSTRACT

Maintenance of a genome requires DNA repair integrated with chromatin remodeling. We have analyzed six transcriptome data sets and one data set on translational regulation of known DNA repair and remodeling genes in synchronized human cells. These data are available through our new database: www.dnarepairgenes.com. Genes that have similar transcription profiles in at least two of our data sets generally agree well with known protein profiles. In brief, long patch base excision repair (BER) is enriched for S phase genes, whereas short patch BER uses genes essentially equally expressed in all cell cycle phases. Furthermore, most genes related to DNA mismatch repair, Fanconi anemia and homologous recombination have their highest expression in the S phase. In contrast, genes specific for direct repair, nucleotide excision repair, as well as non-homologous end joining do not show cell cycle-related expression. Cell cycle regulated chromatin remodeling genes were most frequently confined to G1/S and S. These include e.g. genes for chromatin assembly factor 1 (CAF-1) major subunits CHAF1A and CHAF1B; the putative helicases HELLS and ATAD2 that both co-activate E2F transcription factors central in G1/S-transition and recruit DNA repair and chromatin-modifying proteins and DNA double strand break repair proteins; and RAD54L and RAD54B involved in double strand break repair. TOP2A was consistently most highly expressed in G2, but also expressed in late S phase, supporting a role in regulating entry into mitosis. Translational regulation complements transcriptional regulation and appears to be a relatively common cell cycle regulatory mechanism for DNA repair genes. Our results identify cell cycle phases in which different pathways have highest activity, and demonstrate that periodically expressed genes in a pathway are frequently co-expressed. Furthermore, the data suggest that S phase expression and over-expression of some multifunctional chromatin remodeling proteins may set up feedback loops driving cancer cell proliferation.

1. Introduction

Repair of damage to DNA requires complex biological mechanisms that are tightly regulated and integrated. Damage that is not corrected prior to replication may be cytotoxic and mutagenic, making DNA damage responses during the cell cycle of particular interest. Some proteins have DNA repair as their sole or main function. However, a number of DNA repair proteins also have additional functions, e.g. in adaptive immunity [1], transcription [2] and in replication [3]. Progression of cell cycle processes is normally monitored by distinct checkpoints in G1/S, intra-S and G2/M. These checkpoints control the progression through the various phases of the cell cycle. Although the checkpoints are distinct, they all respond to lesions in DNA and share several proteins [4]. Checkpoint activation and recruitment of DNA damage response proteins depend on the type of lesion [5]. Below we have briefly outlined characteristics of the major DNA repair mechanisms.

Base excision repair (BER) is a highly versatile DNA repair mechanism that corrects a very large number of small base lesions caused

Abbreviations: MMR, mismatch repair; NER, nucleotide excision repair; BER, base excision repair; DSB, DNA double-strand break; NHEJ, non-homologous end joining; HR, homologous recombination; FA, Fanconi anemia; SS, serum starvation; TT, double thymidine block; NZ, nocodazole; MS, mitotic shake off.

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by oxidation, deamination and alkylation. The pathway is initiated by one among 11 known mammalian DNA glycosylases that recognize and remove the damaged base. BER is completed by a short patch or a long patch repair route that in part use different proteins in the downstream steps [6]. Some BER factors are known to be regulated in a cell cycle specific manner. Specifically, expression of uracil-DNA glycosylase encoded by the *UNG* gene peaks in late G1 and S phase both at transcript and protein levels [7–10], whereas thymine/uracil mismatch glycosylase TDG peaks throughout G1 phase and declines in the S phase [9]. However, upregulation of nuclear UNG in G1 phase and strong downregulation in S phase was reported by one group [11]. The reason for this inconsistency is not known.

Mismatch repair (MMR) corrects base-base mismatches and insertion/deletion loops generated during DNA replication and recombination. Since MMR is an immediate post-replicative correction mechanism, a prediction would be that the proteins involved are cell cycle regulated. Some key factors in MMR, e.g. MSH2 and MLH1 proteins were indeed reported to be upregulated when quiescent cells were stimulated to proliferate, but fluctuation through cell cycle phases was less clear [12,13]. MMR also requires several replication factors, such as DNA polymerases, EXO1, RFC and PCNA [14].

Nucleotide excision repair (NER) is the principal repair mechanism for DNA damage causing helix distortion, most commonly pyrimidine dimers from ultraviolet light, and requires more than 30 gene products, some unique and other shared with DNA replication and transcription [15].

Double strand breaks (DSBs) are highly toxic lesions that may cause various mutations, deletions and oncogenic translocations. They may be caused directly by ionizing radiation, or indirectly by endogenous or exogenous challenges that cause single stranded breaks that, unless repaired, are converted to DSBs upon replication. Repair of DSBs in mammalian cells takes place by non-homologous end joining (NHEJ) or related alternative mechanisms in all cell cycle phases and in addition by homologous recombination (HR) repair during S phase and G2 phase, when a sister chromatid is available [16,17].

Interstrand crosslinks (ICLs) may be formed by environmental mutagens, as well as a number of chemotherapeutic drugs. ICLs represent a highly toxic type of lesion, the processing of which requires input from several repair mechanisms, including NER, HR, MMR, NHEJ, translesion polymerases and, importantly, a number of Fanconi anemia (FA) proteins. Deficiency in FANC-proteins is associated with high sensitivity to agents that cause ICLs. Furthermore, repair of ICLs may use different mechanisms in different cell cycle phases [18].

Methods for cell cycle synchronization include temporary growth arrest in the G1/G0-phase at high cell density or serum starvation, as well as block of cell cycle progression at the G1/S phase transition or in the G2 phase. Alternatively, enrichment of cells in certain cell cycle phases without chemical treatment may be obtained by mitotic shake off, elutriation centrifugation or by other means. These methods all have advantages and drawbacks, including limited synchrony, cell line-specific differences, intraculture heterogeneity, toxicity of chemicals changing expression, small yield of cells and requirement for specialized instrumentation. It is advantageous if cultures can be followed through two or more rounds of the cell cycle and the method should ideally fulfill a set of defined criteria [19]. For example, the growth as well as the integrity of the cells should not be affected by the synchronization process [19]. A good synchronization also requires limited increase in cell number between each successive division [19]. To investigate genome-wide expression of cell cycle-associated genes, microarray analyses of synchronized cells have been carried out using different eukaryotic cell lines [20–25]. Results from cell cycle studies show that functionally distinct classes of genes are expressed at the highest level when they are needed [25–27]. Whereas the regulation of protein complexes frequently has evolved differently in different species, regulated subunits of proteins or complexes are usually expressed just before their time of action. Furthermore, changes in transcriptional regulation have frequently co-evolved with post-translational control [26].

Here we have used available data sets to examine transcription profiles and translational regulation of all known human DNA repair and chromatin remodeling genes during the cell cycle. These data sets use different synchronization procedures and cell lines, which reduce the risk of method-associated errors. Periodic expression of transcripts does not prove that protein levels fluctuate correspondingly. However, from a number of earlier studies, expression at transcript and protein levels of several DNA repair and remodeling genes are known [25,27–30]. Reassuringly, our results are in good agreement with these results, as discussed below. Furthermore, DNA repair and remodeling often use multi-subunit proteins or complexes to carry out the task. Based on available information [26], it may be fair to hypothesize that if at least one of the required and critical subunits in a protein or protein complex is clearly cell cycle regulated, the function of the protein or complex is likely to be cell cycle regulated. Our studies identify a number of DNA repair and chromatin remodeling genes that are cell cycle regulated, most commonly peaking in the G1/S or S phase. Furthermore, the information identifies gene sets that likely contribute to overall regulation of pathways and subpathways.

2. Materials and methods

2.1. DNA repair and chromatin remodeling genes

A list of 177 DNA-repair genes published previously [31,32] was used and supplemented with additional *bona fide* DNA repair genes identified by PubMed searches, to give a sum of 345 DNA repair genes. The list of established and putative genes for chromatin remodeling proteins contains 99 genes. They were compiled from a comprehensive literature search carried out by members of the FANTOM5 consortium (EpiGenes 1.3; F. Drabløs, Y. Medvedeva, A. Lennartsson, unpublished data) and supplemented with novel information from data searches. The new database named "Cell Cycle Regulation of DNA Repair and Chromatin Remodeling Genes" is found here: www.dnarepairgenes.com. We have consistently used the HUGO Gene Nomenclature Committee (HGNC) approved gene names in the new database, as well as in the paper. The alternative names can be found in OMIM.

2.2. Data sets in the novel database

Seven time series gene expression data sets from five different studies were downloaded and analyzed. These include primary foreskin fibroblasts synchronized in G0-phase by serum starvation [20]; HaCaT cells, a near diploid keratinocyte cell line, synchronized at G1/S-transition by double thymidine block [22]; human cervical carcinoma HeLa cells synchronized in M by nocodazole [22] or in G1/S transition by double thymidine block (this paper, see Supplementary Materials); HeLa cells using double thymidine block and nocodazole [33]; or HeLa cells synchronized by double thymidine block, nocodazole and mitotic shake-off [25]. These studies, except [33], were carried out using gene expression microarrays to analyze multiple time points during one or several cell cycles. The single data set available on translational regulation in HeLa cells by ribosome profiling using RNA sequencing, as well as the accompanying transcriptome, were based on three time points only (G1, S and G2) [33]. These therefore do not discriminate between genes expressed

in early/middle G1, and genes expressed at the G1/S transition. Note that as this study specifically measured changes in translational rates relative to transcriptional levels, some genes were identified as translationally regulated in all three phases.

2.3. Analysis of transcript profiles

Cell cycle regulated genes were identified using partial least square (PLS) regression on to a sine and cosine function with periods equal to the specific cells' cell cycle duration as estimated by flow cytometry analyses of DNA content. PLS regression is a dimension reduction technique that tries to find the main principal directions in the data that explain the main variation in the response. In this case, the data are the gene expression profiles at the different cell cycle time points and the response are the values of the sine and cosine curves at the corresponding time points. The main reason for using regression on to sine and cosine functions is that these functions are ideal for modeling the expected cyclic expression profiles of cell cycle regulated genes. Moreover, as the sine and cosine functions are orthogonal functions, the first and second principal components of the PLS regression will form an abstract phase diagram where the phase angle and distance from the origin of each gene can be directly interpreted as the gene's peak point in the cell cycle and the peak's relative height, respectively. Based on this phase angle, each gene was assigned a cell cycle phase by comparing its phase angle to those of a small set of genes with previously well-described cell cycle profiles, as described [22].

Transcription data from Stumpf et al. [33] were analyzed by using TopHat [34] and Cufflinks [35] followed by EBSeq in R [36] to compare the three individual time points, one from each cell cycle phase. Specifically, TopHat was used to map the sequence reads to the human genome. The expression of each gene was determined using Cufflinks that counts the number of reads that match to a given RefSeq transcript. EBSeq was used to determine differential expressed transcripts between the cell cycle phases. EBSeq uses the output from Cufflinks and estimates expression differences for all gene isoforms.

3. Results and discussion

3.1. Organization of the new database "cell cycle regulation of DNA repair and chromatin remodeling genes"

The screen shot shows key features of the novel database on cell cycle regulated DNA repair genes and chromatin remodeling genes (Fig. 1). The horizontal menu line displayed in the figure can be used to maneuver to any part of the database. The ARTICLE will contain the published form of the present paper. The GENE LIST lists all identified DNA repair genes and chromatin remodeling genes separately, both cell cycle regulated and not cell cycle regulated ones. By clicking on the name of individual genes, information in OMIM is available. The banner CELL CYCLE lists the cell cycle regulated DNA repair and chromatin remodeling genes, as separate lists, with reference to source of the data sets. Each gene has been assigned to the cell cycle phase in which it has the highest expression in each of the studies included. A transcriptome expression profile for each gene, based on data from our laboratory [22], foreskin fibroblasts [20], and this paper (listed as Mjelle et al., 2014 in the database; see also Supplementary Materials and Supplementary Fig. 1), can be reached by clicking on the gene name. Expression data from the other studies [25,33] can be reached by clicking METHODS in the menu line and then the relevant study.

3.2. Results of the analyses – overview

To reduce false positives, we limited detailed transcriptome analyses [20,22,25,33] to genes that were cell cycle regulated in at least two data sets. For analyses of translational regulation, the single data set available was used [33]. In sum, when analyzing the transcriptome data sets for which expression profiles is displayed in the novel database, we observe an enrichment of DNA repair genes among cell cycle regulated genes (17% compared to 8% for all genes, $p = 5.7e{-}9$), whereas the number of cell cycle regulated chromatin remodeling genes is not higher than expected (11% compared to 8% for all genes, $p = 0.27$). More detailed information, including expression profiles, is found in the novel database: www.dnarepairgenes.com. This page gives information for different cell lines, cell cycle phase of highest expression (with links to expression profiles), chromosomal localization of the genes and known and presumed gene functions (links to OMIM).

It should be understood that although many genes may be upregulated several-fold in distinct cell cycle phases, a low level of expression is usually observed in other cell cycle phases. Normal primary fibroblasts have the highest number of cell cycle regulated genes (80 genes) suggesting that cell cycle regulation of several genes involved in DNA repair may be deranged in transformed cells. This could not be explained by reduced synchrony in HaCaT and HeLa cells (Supplementary Figure 1). In total, we identified 124 DNA repair genes to be cell cycle regulated in at least one data set, whereas 58 were cell cycle regulated in two or more data sets. Genes with conserved expression profiles across experiments are most frequently expressed in late G1 phase and S phase, although some have distinct expression in other cell cycle phases, e.g. TOP2A and ASF1A which are G2 phase regulated.

Although expression profiles differ significantly between cell lines, there is a reasonable overlap between the studies using transcription profiling as tool. Furthermore, the relationship between expression at the transcription level and protein level is known for some DNA repair and remodeling genes. It is reassuring to notice that transcript levels generally agree very well with protein data (when known). Some examples include G1/S genes *UNG* [10], *PCNA* [37], *POLD* and *POLA* [38], *BLM* [39], *BRCA1* [40], *FEN1* [41], *HELLS* [42], *CHAF1A* and *CHAF1B* [43], but also the G2 expressed gene *TOP2A* [44,45]. In some cases the expression is upregulated both transcriptionally and translationally in the same cell cycle phase, e.g. MSH6, ATAD2 and POLA1, which are upregulated in G1/S or S phase. There are also several examples of genes that are either transcriptionally or translationally regulated. More detailed analyses are found below.

3.3. Translational regulation in the cell cycle

In total, 30 DNA repair genes and 11 chromatin remodeling genes were found to be translationally regulated in the cell cycle. They were mostly upregulated, although three were downregulated, either in the G1 phase (BTG2 and Tp73) or S phase (PAPD7). Thus, translational regulation is relatively common and predominantly acts as a mechanism for upregulation of genes in a cell cycle phase. Among the DNA repair genes, 13 were only translationally regulated (e.g. KAT5, SMC3, ERCC4 and GTF2H2). KAT5 (a histone Lys acetyltransferase, initially called TIP60), is translationally upregulated in G1 phase and contributes to DSBR. KAT5 acetylates ATM via chromatin binding and activates the ATM-pathway [46]. SMC3 (structural maintenance of chromosomes 3) is translationally upregulated in G1 and S phase. It is part of the cohesion complex that keeps sister chromatids together and it is important for DSBR by homologous recombination [47]. ERCC4 (also called XPF) is translationally upregulated in all three phases examined (G1, S, and M) and, strictly speaking, not cell cycle

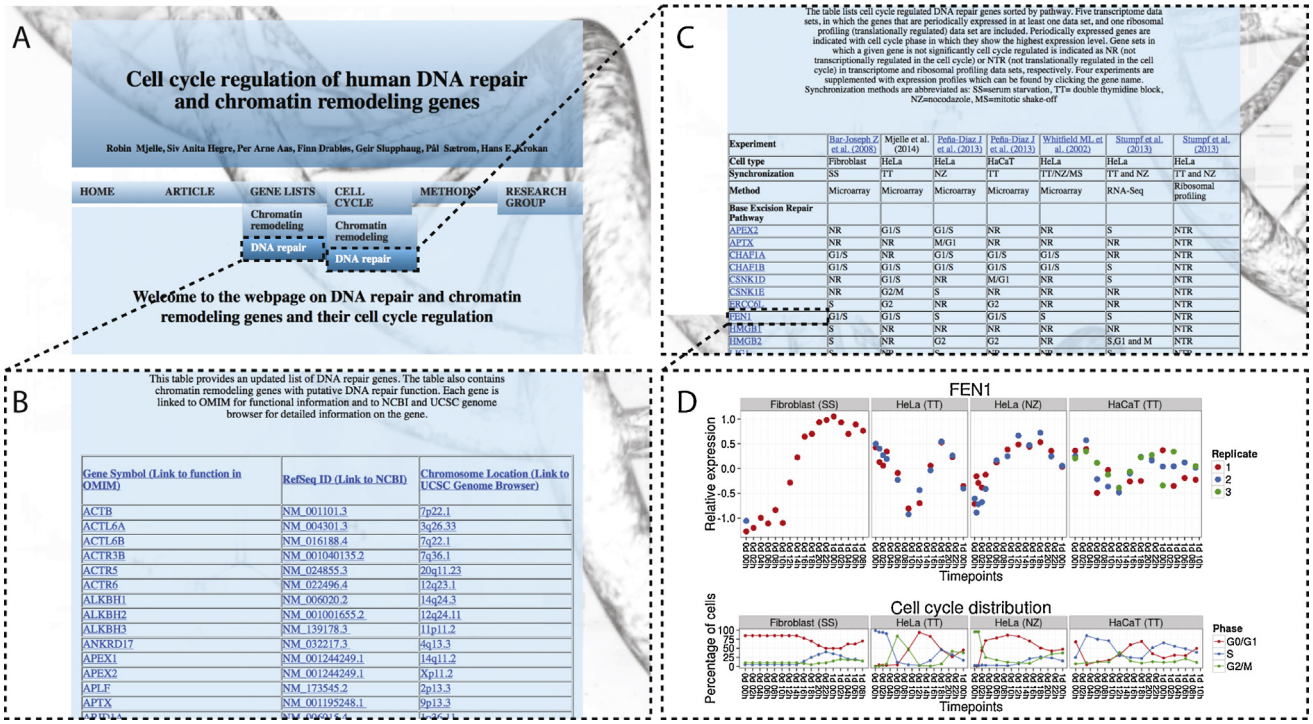

Fig. 1. Overview of the database's key features. (A) The database's main page (HOME) has a menu that provides links to background information about the database (ARTICLE, METHODS, RESEARCH GROUP) and links to the database's main sections, which are the lists of chromatin remodeling and DNA repair genes (GENE LISTS) and their cell cycle expression profiles (CELL CYCLE). (B) The "GENE LISTS" pages provide links to information about each gene's function and genomic context. Chromatin remodeling and DNA repair genes have separate pages; shown here is an excerpt of the DNA repair genes. Note that some multifunctional genes, such as HELLS or TOP2A, are present on both. (C) The "CELL CYCLE" pages show chromatin remodeling and DNA repair genes with significant cell cycle dependent regulation in at least one of the seven datasets examined. Abbreviated cell cycle phases (G1/S, S, G2, G2/M, and M/G1) show the phase in which a gene has its peak expression. The abbreviations NR and NTR indicate datasets in which the gene was not detected to be transcriptionally or translationally regulated, respectively. Chromatin remodeling and DNA repair genes have separate pages; shown here is an excerpt of the DNA repair genes, which are grouped by DNA repair pathway. Each gene links to a figure (D) that shows the gene's expression profile and the cell cycle phase distribution for the first four experiments listed in the table. (D) The expression profiles of FEN1.

regulated. ERCC4 is best known for its function as a structure-specific endonuclease in complex with ERCC1 in NER, but is also involved in ICL repair and DSBR [48]. GTF2H2, a subunit of TFIIH, is translationally upregulated in G1 phase and is required both for NER and transcription.

3.4. Genes encoding base excision repair (BER) and single strand break repair (SSBR) proteins

The damage recognizing proteins in BER are DNA glycosylases that remove damaged bases that do not cause major distortion to the DNA helix structure. SSBR is generally using proteins involved in the downstream steps of BER, although this may be a simplistic view. The 11 human DNA glycosylases identified recognize both spontaneous and induced lesions. Four of the genes encoding DNA glycosylases were found to be cell cycle regulated; these are *UNG, TDG, NTHL1* and *NEIL3. UNG* and *NTHL1* are expressed at G1/S, NEIL3 in S/G2 and TDG in G1. In addition, UNG is translationally upregulated in G1. We found no evidence for cell cycle regulation of *MPG*, *SMUG1*, *MBD4*, *NEIL1*, *OGG1* and *MUTYH* (Fig. 2). However, evidence for S phase expression was previously reported for *NEIL1* when using prolonged serum starvation to synchronize fibroblasts [49]. The opposite expression pattern of UNG and TDG has been reported previously, both at the mRNA and protein levels [9] and our results are consistent with previous findings [9,50,51]. The G1/S expression of *UNG* is consistent with its defined role in immediate post-replicative removal of misincorporated dUMP [10,52], as well as its probable role in pre-replicative correction of U:G mismatches [53]. Nuclear UNG2 (encoded by *UNG*) and NEIL1 (and NEIL3), unlike other DNA glycosylases, are highly active on single-strand and double-strand DNA and are located in replication foci during S phase [54]. Possibly, UNG2 and NEIL1 may remove damaged bases in single-stranded DNA at the replication fork, followed by fork regression and BER by the usual mechanism for double-stranded DNA, as suggested [53,54]. *NEIL3* was recently reported to be induced in late S phase in cells synchronized by density inhibition, but the data reveal that *NEIL3* expression continues into G2 [55], thus these data are consistent with our results. Several genes involved in downstream steps of short-patch are not cell cycle regulated, including *POLB*, encoding DNA polymerase β, *POLL*, encoding DNA polymerase λ, *APEX1*, encoding AP-endonuclease 1 and *PNKP*, encoding polynucleotide kinase phosphatase. Interestingly, PARP1 and PARP2 are S phase regulated in normal fibroblasts, consistent with a role of PARP in SSB and at least some forms of BER, but apparently not all [56]. The genes for proteins in the downstream steps of long-patch BER (*LIG1*, *PCNA*, *FEN1*, *POLD1*, *POLD3*, *POLE* and *POLE2*), are all consistently S phase or G1/S regulated. All proteins from these genes are also replication proteins. LIG1 is involved in short patch repair as well, whereas LIG3 is probably involved in nuclear short patch BER and essential for mitochondrial BER (reviewed in [6]). These results support a model where long patch BER is mainly acting in proliferating cells and that repair by long patch BER is carried out by genes induced in late G1 and early S phase, in agreement with previous results on in vitro BER in cell extracts [57]. The S phase expressed *POLA1* encodes DNA polymerase α/primase and has relatively low fidelity due to lack of $3' \rightarrow 5'$ proofreading activity. It is not thought to be involved in BER but appears to be involved in repair of SSBs during replication through binding of XRCC1, presumably near the replication fork [58].

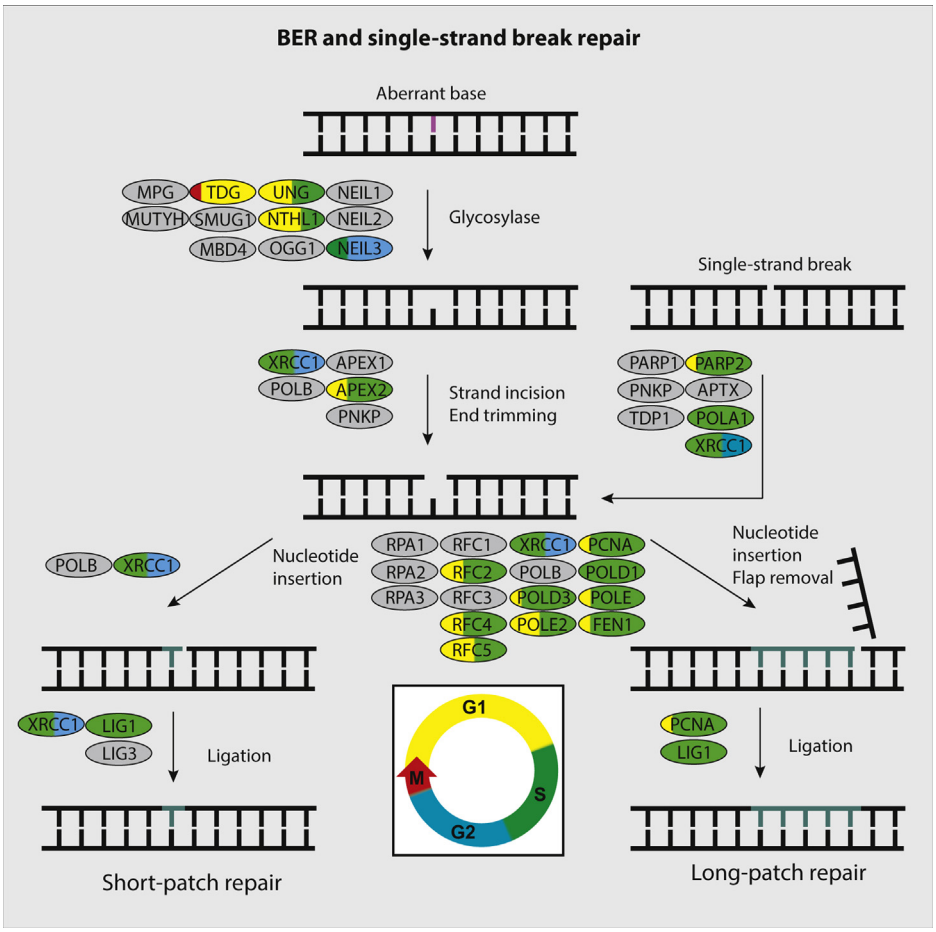

Fig. 2. Cell cycle regulated genes in the BER pathway. The genes are marked with colors according to which cell cycle phase they have highest expression, as indicated in the figure. Only gene products shown to be cell cycle regulated in at least two transcriptome studies, or translationally regulated [33] are colored. Note that gene products have not been assigned to complexes, merely stage at which they are thought to be involved. Gray fill in ovals indicate that the genes are not found to be cell cycle regulated (not all shown).

3.5. Genes encoding proteins involved in direct repair of base lesions

Generally, genes encoding proteins involved in direct repair of base alkylations are not cell cycle regulated (Fig. 3). This applies to *MGMT* required for repair of the highly mutagenic DNA lesion O^6-methylguanine, as well as human AlkB homologues *ALKBH1*, *ALKBH2* and *ALKBH3*. *ALKBH2* was cell cycle regulated to G1 phase in one HeLa cell strain and S in another, but not cell cycle regulated in fibroblasts and HaCaT cells. Since alkylation lesions may occur at all cell cycle stages from normal metabolites (e.g. S-adenosylmethionine) as well as external challenges, the general absence of cell cycle regulation of these genes would be an expected outcome.

3.6. Genes encoding nucleotide excision repair (NER) proteins

NER is required for excision repair of bulky DNA adducts, e.g. from ultraviolet light. Genes for repair proteins involved in the initial steps in NER by both global genome repair (GGR) and transcription coupled repair (TCR) appear to be expressed independently of cell cycle phases, although most genes in the downstream steps are upregulated in S phase (Fig. 4). Thus, CSA (*ERCC8*) and CSB (*ERCC6*) required for TCR, are not detected as cell cycle regulated at the transcript level, neither are the XPC-RAD23B-complex in GGR or any of the other XP-genes, including *XPA*, *XPB* (*ERCC3*), *XPD* (*ERCC2*), *XPE* (*DDB1*), *XPF* (*ERCC4*) or *XPG* (*ERCC5*). However, ERCC4 is translationally upregulated in G1, S and M. Furthermore, the final steps of the pathway, which are in part shared with DNA replication and other excision repair pathways, use cell cycle regulated genes that are most frequently upregulated during G1/S phase, including *RPA1*, *PCNA*, *RFC4* and *RFC5* (subunits of RFC), *LIG1*, *POLD1* and *POLD3* (subunits of POLδ) and *POLE* and *POLE2* (encoding POLε). In addition, *POLK* (encoding POLκ) is translationally upregulated in the S phase. For gap filling, ubiquitinated PCNA recruits POLκ to the site of DNA damage, where it is found in complex with POLδ. These polymerases are responsible for synthesis of approximately half of the repair gap and POLε the rest [59]. Furthermore, UV-induced nuclear import of XPA primarily takes place in the S phase and appears to initiate NER in a p53-dependent manner [60]. The NER endonuclease XPG and the closely related yeast homolog Rad2 have a PCNA-binding domain in the C-terminal region. The Rad2-PCNA interaction was recently found to mediate arrest of cell cycle progression, suggesting a role of XPG/Rad2 other than the established endonuclease function [61].

3.7. Genes encoding mismatch repair (MMR) proteins

MMR proteins are primarily required for correction of mismatches from replication errors. Some studies have reported cell cycle dependent expression of MMR genes while others have noted just moderate fluctuations throughout the cell cycle [12,62,63]. We observe that the genes encoding major components in mismatch recognition are transcriptionally up-regulated in S or G1/S phase

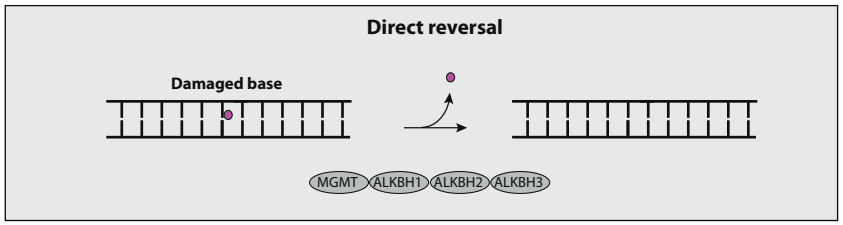

Fig. 3. Genes for direct base repair are not cell cycle regulated.

in normal fibroblasts, including *MLH1, MSH2* and *MSH6. MSH6* is upregulated in S phase in all cell lines, whereas the other components are less consistently upregulated. In addition, *MSH2* and *MSH6* are translationally upregulated in G1/S or S phase (Fig. 5). *MSH3* is apparently not cell cycle regulated. Generally, MSH heterodimers recognize mismatches, whereas MLH heterodimers are strand-specific endonucleases. The MSH2-MSH6 complex (MutSα) recognizes single nucleotide mismatches, whereas the MSH2-MSH3 complex (MutSβ) recognizes insertion/deletion loops. MutL homologues PMS1 and PMS2 form heterodimers with MLH1. Among these, PMS2 is translationally upregulated in G1. MSH4 and MSH5, the expression of which is normally largely limited to ovary and testis, are not cell cycle regulated in the cell lines examined. The MSH4-MSH5 complex recognizes Holliday junctions and forms a sliding clamp during meiosis, but has no apparent role in replication-associated MMR, thus there is no specific requirement for these components during S phase [64]. The gene encoding the 5′ → 3′ excision nuclease EXO1, required for damaged strand excision in MMR is upregulated in G1/S or S phase. EXO1 has multiple functions in DNA maintenance, including MMR, replication, recombination and telomere maintenance, processes that are all associated with S phase in mammalian cells. As expected, other replication-related genes active in re-synthesis and ligation are upregulated during S phase, including *RFC3*, *RFC*4, *RFC5*, *PCNA*, *RPA1*, *POLD1*, *POLD3* and *LIG1*. Thus, expression patterns of genes for MMR proteins collectively comply with their roles in MMR, HRR and replication.

3.8. Genes encoding Fanconi anemia (FA) pathway proteins

FA proteins have a major role in repair of inter-strand cross links (ICLs). FA is associated with increased cancer risk and cellular sensitivity to inter-strand crosslinking agents and ionizing radiation [65]. The majority of FA genes are upregulated in G1/S at the transcript level in at least two data sets (11 genes) or translationally upregulated in the S phase (3 genes). Repair processes requiring FA

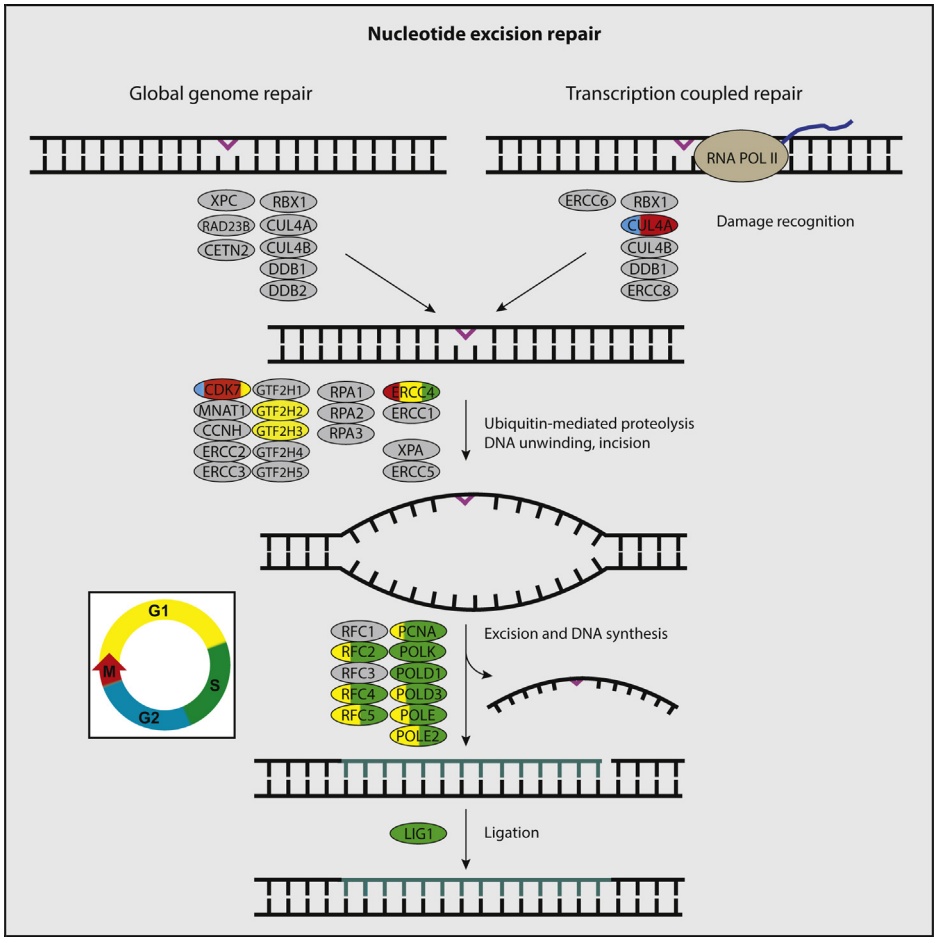

Fig. 4. Cell cycle regulated genes in the NER pathway; see Fig. 2 for an explanation of the color codes. Genes initiating NER.

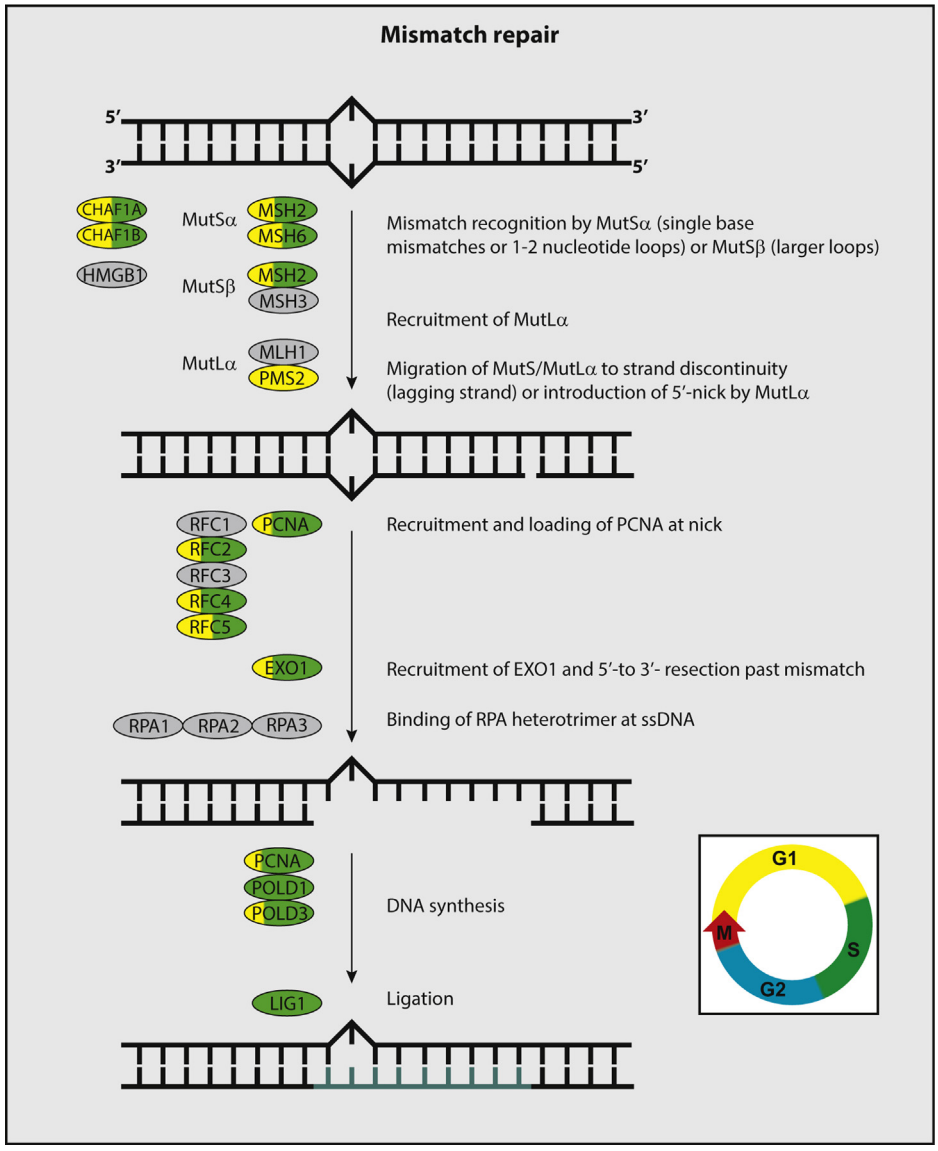

Fig. 5. Cell cycle regulated genes in the MMR pathway; see Fig. 2 for an explanation of the color codes.

proteins are not limited to ICLs, although they apparently have a critical role there. The FA pathway is damage-inducible by replication fork-stalling lesions that activate ATR kinase, which in turn activates some proteins in the FA core complex. The FA pathway is complex and involves 13 FANC genes (FANC A, B, C, D1, D2, E, F, G, I, J, L, M and N) and other genes as well, including the S phase expressed genes *BLM* (helicase), *USP1* (deubiquitinase), *BRCA1*, *RPA1*, *RAD1* and *RAD51*. Genes for most components in the FA core complex (*FANC A, B, E* and *L*, but not *C* and *F*) are up-regulated during S phase (Fig. 6). Although *FANCM* is not S phase expressed at transcript level, it is translationally upregulated in the S phase. Upon activation, the FA core complex ubiquitinates the I–D2 complex consisting of FANCI and FANCD2, which are apparently transcriptionally up-regulated during late S- and G2-phase. The I-D2 complex is required to promote repair by homologous recombination, which in mammalian cells takes place in the S- and G2 phase. The I-D2 complex in turn activates the downstream components BRCA2 (FANCD1), RAD51 and RAD51C, among which the critical damaged DNA-binding protein RAD51 is upregulated during G1/S- and S phase. FAN1 (Fanconi anemia associated nuclease 1) is required for ICL repair, but is not cell cycle regulated [66]. However, the FA complex may also be activating the MMR pathway through the interaction with FAN1, MLH1 and PMS2 [66], among which MLH1 is upregulated in S phase, and PMS2 translationally upregulated in G1. In conclusion most of the FA proteins and some associated proteins are S phase regulated, in agreement with the view that repair of ICLs is most efficient in the S phase.

3.9. Genes for homologous recombination repair (HRR)

In mammalian cells, HRR is restricted to the S phase and G2 phase, using the sister chromatid rather than the homologous chromosome for strand exchange [17]. Consistent with this, many of the genes involved in HRR are most highly expressed in S phase. Homologous recombination is initiated by the MRN complex consisting of MRE11A, RAD50 and NBN (NBS1). Among these, *MRE11A* is found to be induced in late S- and G2 phase whereas *NBN* is induced in G1 and G1/S (Fig. 7). Furthermore, PARP1 apparently has a role in facilitating HRR at DSBs resulting from collapsed replication forks by binding to DNA ends and inhibiting competitive binding of Ku70/80 and thereby preventing less accurate repair by NHEJ [67,68]. We do not find PARP1 convincingly cell cycle regulated, although it is upregulated in the S phase when fibroblasts are released from serum starvation. One function of PARP1 in HRR may be

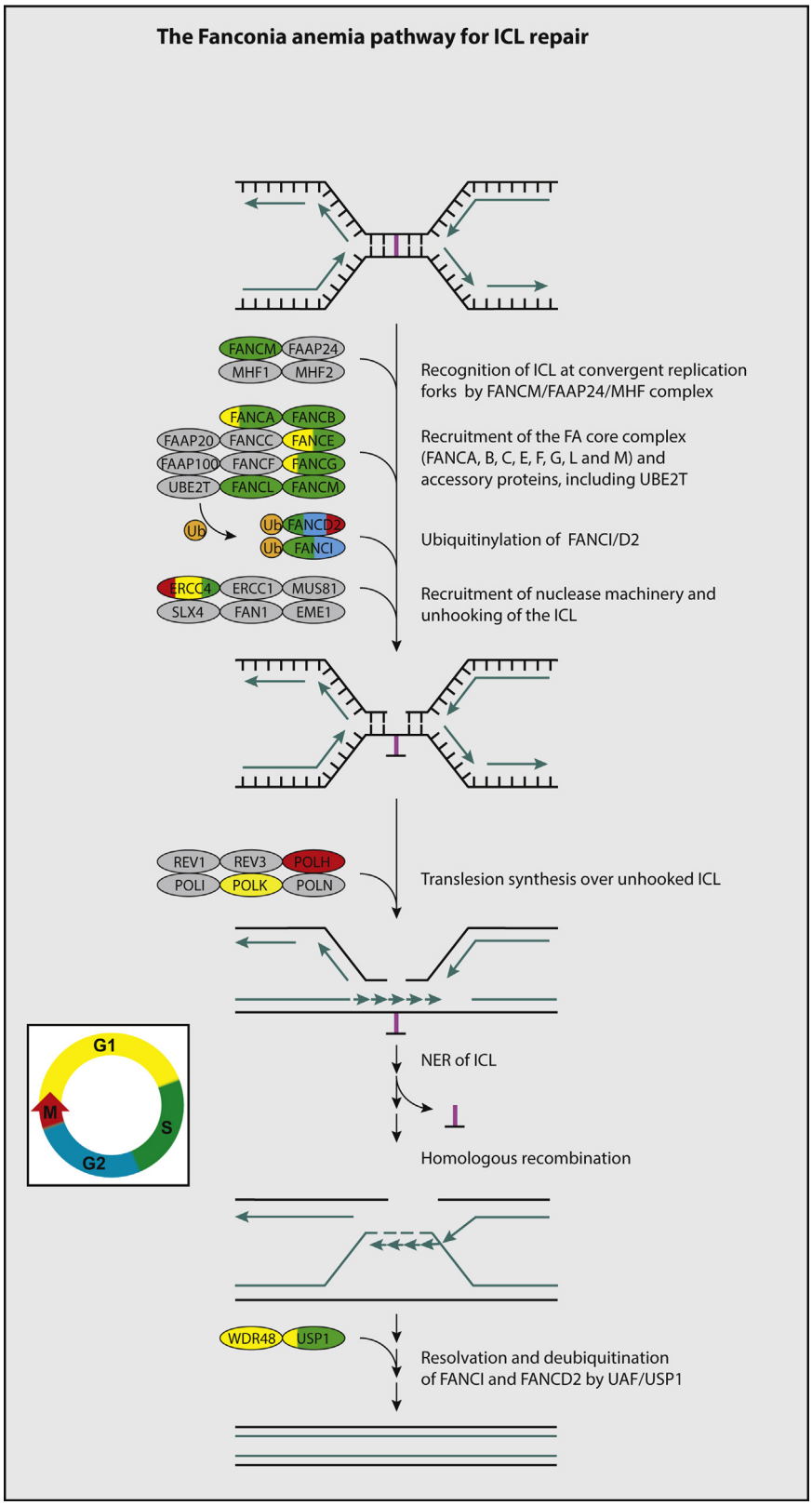

Fig. 6. Cell cycle regulated genes in the FA pathway; see Fig. 2 for an explanation of the color codes.

recruitment of the heterodimer of BRCA1 and BARD1, each of which S phase-regulated. This recruitment is parylation-dependent [69]. In addition, SMC3 is translationally upregulated in G1/S, but not transcriptionally regulated. SMC3 is part of the cohesion complex that keeps sister chromatids together and is important for DSBR by HR [47]. Homology search and DNA-strand invasion is performed by RAD51, which is upregulated during G1/S and S phase across three cell lines. The gene encoding RAD54, a RAD51-interacting protein required for stabilizing RAD51, is also up-regulated during S phase. RAD51-mediated strand exchange was found to be

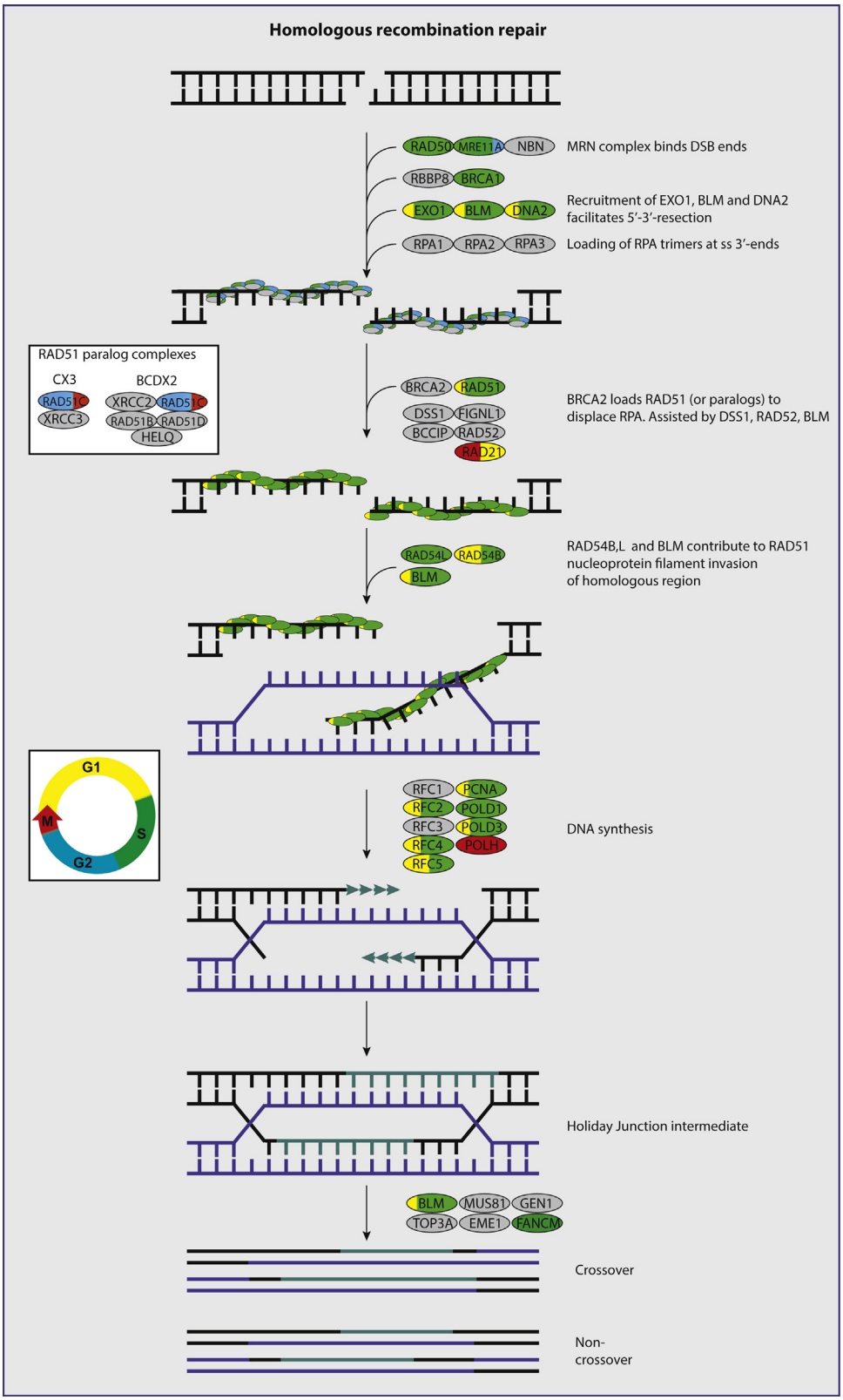

Fig. 7. Cell cycle regulated genes in the HRR pathway; see Fig. 2 for an explanation of the color codes.

stimulated by the PSMC3IP-MND1 complex. PSMC3IP (also called HOP-2) is expressed in G1/S and was recently reported to have a regulatory role both in DSBR and recombination [70]. A recently described RAD51 interaction partner, FIGNL1 [71], interacts specifically with RAD51 and is upregulated in the S phase, similar to RAD51. Of the genes in the post-synapsis step, *BLM* [72] is found to be up-regulated in S phase in all four cell lines and *BRCA2* is possibly upregulated during G2 phase (in fibroblasts only). In conclusion, many of the genes required for HRR are upregulated in S phase, consistent with the activity of this process in the S phase.

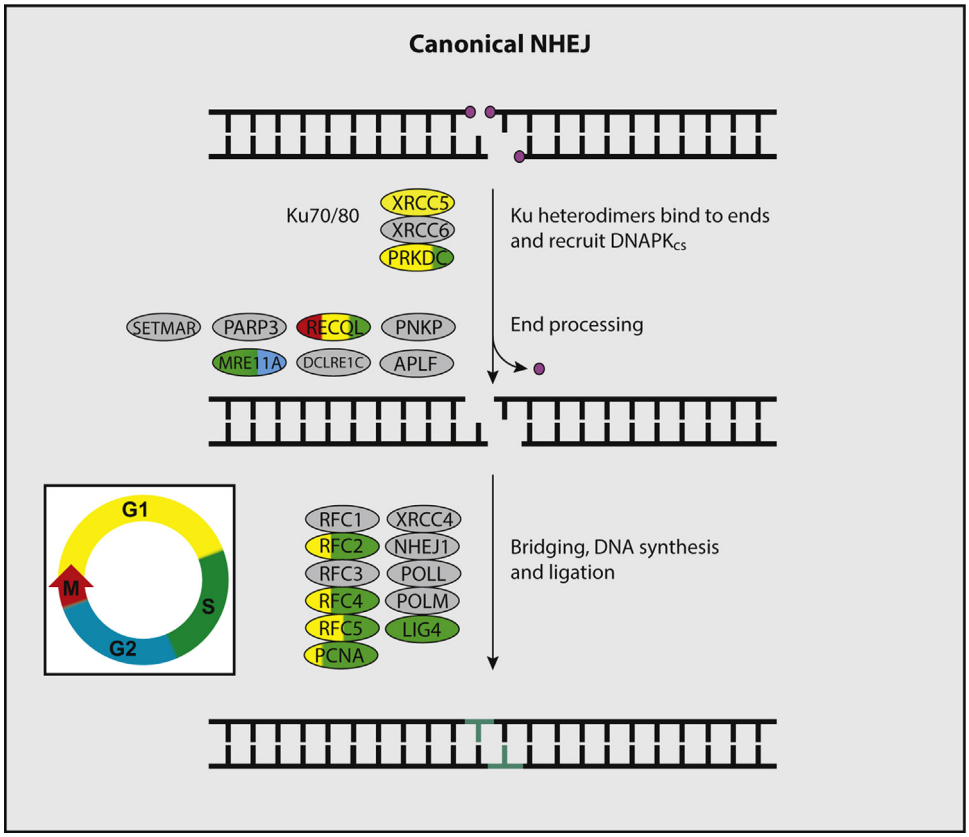

Fig. 8. Cell cycle regulated genes in the NHEJ pathway; see Fig. 2 for an explanation of the color codes.

3.10. Genes encoding proteins for non-homologous end joining (NHEJ) – a regulatory role for PTTG/securin

Generally, genes centrally involved in NHEJ were found not to be cell cycle regulated (Fig. 8). However, *PTTG1*, encoding the 202 amino acids protein PTTG1 (also called securin), consistently had the highest transcript level at the M/G1-transition in all data sets and then declines rapidly during the G1 phase. PTTG1 is a multifunctional and rather intriguing protein. It binds directly to Ku70 (also called XRCC6) and functions as a negative regulator of NHEJ [73,74]. Thus, PTTG1 may inhibit illegitimate NHEJ until completion of replication. It was reported that PTTG1 is ubiquitinated at metaphase-anaphase transition by the E3 ligase anaphase-promoting complex (APC). It is then normally rapidly degraded in proteasomes (reviewed in [75]), thus alleviating the NHEJ-inhibition and reestablishing the capacity for NHEJ during G1 phase. Importantly, PTTG1 also controls sister chromatid separation during mitosis by binding to and inhibiting separase, which when active cleaves cohesin that holds sister chromatids together [76]. Normal levels of PTTG1 may prevent premature sister chromatid separation, thus facilitating DNA repair by HRR during the S phase and G2. However, overexpression of PTTG1 correlates strongly with aneuploidy in breast cancer [77], possibly due to an inability of sister chromatids to separate. Overexpression of PTTG1 is associated with a wide range of malignancies, e.g. hematopoietic malignancies [78], colon cancer [79] and breast cancer [80]. Thus, while PTTG1 normally regulates several processes important to genomic stability, overexpression appears to promote genomic instability, stimulate proliferation and contribute to carcinogenesis. PTTG1 also functions as a transcriptional regulator of several genes involved in tumorigenesis [81]. We conclude that normally the transcript level of PTTG1 is upregulated at the M/G1-transition, but subsequently ubiquitinylated and degraded in proteasomes at metaphase-anaphase transition, allowing chromatid separation. Overexpression of PTTG1 apparently results in inability of sister chromatids to separate with increased risk of aneuploidy in cancer cells [82,83].

3.11. Chromatin assembly and remodeling in DNA repair

Chromatin remodeling complexes temporarily disrupt and remodel DNA–nucleosome interactions, thus facilitating different DNA transactions, including DNA replication, transcription and repair [84,85]. We examined 99 genes thought to be involved in chromatin remodeling, many of which are already known to have a function in DNA repair. Among these, 39 were found to be cell cycle regulated in at least one transcriptome data set and 11 in at least two data sets. While three remodeling genes were regulated both at the transcriptional and translational level, several were only translationally regulated (CHD1, ACTL6A, ZRANB3, TP73, SMARCA1, SMARCA5 and SMARCAD1). The cell cycle regulated chromatin remodeling genes were largely G1/S-expressed genes, except TOP2A, which displayed highest expression in G2 phase.

The CAF-1 (chromatin assembly factor 1) complex consists of CHAF1A, CHAF1B and p50 and is generally required to assemble nucleosomes after DNA synthesis. We find that *CHAF1A* and *CHAF1B* are consistently most highly expressed in G1/S. CAF-1 has a role in MMR, which itself has the major normal function in the S phase. In MMR the long repair patch is generated by the S phase-regulated 5′–3′ nuclease EXO1 [14]. After DNA re-synthesis in MMR, the CAF-1 complex is required to re-assemble nucleosomes, protecting DNA from excessive degradation [86,87]. CAF-1 is also required to restore chromatin after NER [88] and HRR [7], and is thus heavily involved in DNA repair processes.

Genes for the putative ATPases/helicases ATAD2 (also called ANCCA) and HELLS (also called LSH, PASG and SMARCA6) are also

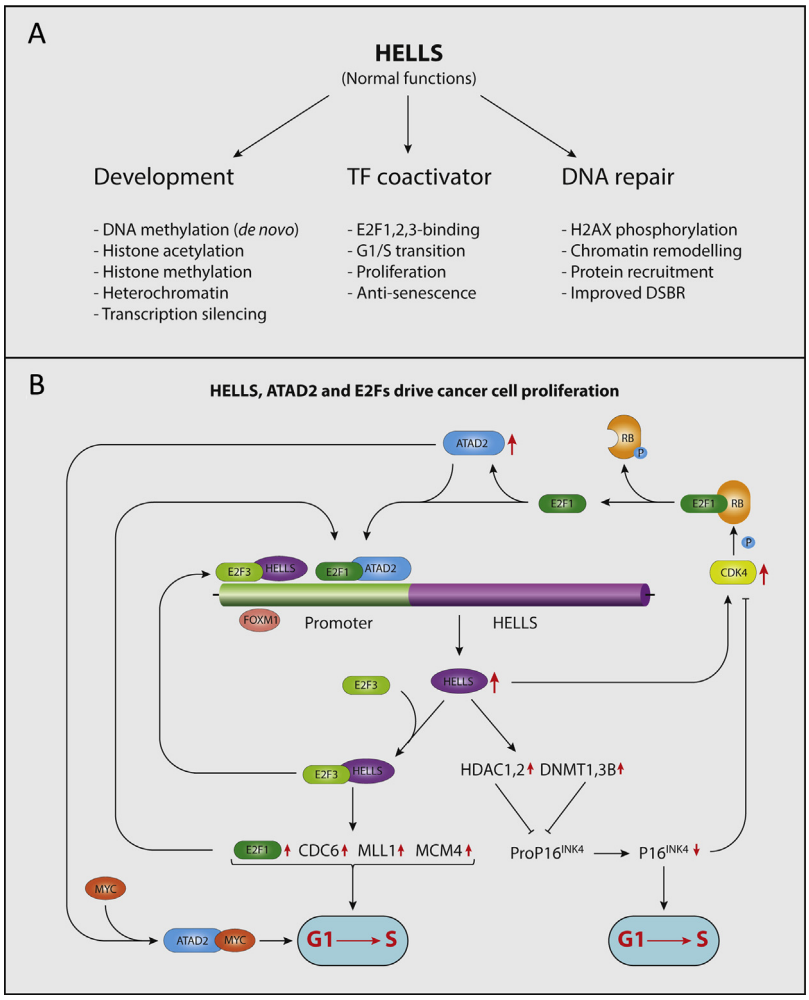

Fig. 9. Model for functions of HELLS – a multifunctional putative helicase and proliferation driver. (A) HELLS, has functions in development (epigenetics), as E2F co-activator in transcription to stimulate cell growth, as well as in repair of DSBs through increasing phosphorylation of H2AX to generate γH2AX. (B) Overexpressed HELLS, ATAD2 and E2Fs may set up functional loops that make them drivers of tumor cell proliferation. They are all S phase expressed and frequently overexpressed in tumors. HELLS and ATAD2 are known to interact physically with E2Fs and function as co-activators of E2F-mediated transcription for a number of genes (but not necessarily *all* genes that use E2F as transcription factor). HELLS has been shown to mediate epigenetic silencing of $P16^{INK4}$ expression, thereby causing activation of CDK4, phosphorylation of RB and release of active E2F1. In sum, HELLS, ATAD2 and E2Fs mediate expression of several genes that stimulate G1/S-transition and cell proliferation.

consistently most highly expressed in G1/S. In addition, ATAD2 is translationally upregulated in the S phase. HELLS has a documented function in DSBR [89], and ATAD2 is likely to be involved in DNA repair. HELLS and ATAD2 are overexpressed in several cancer types and are considered as proliferation drivers. HELLS and ATAD2 are significantly coexpressed, with a Pearson correlation coefficient of 0.63 when analyzed using the database COEXPRESdb [90]. Through various interactions and diverse functions they have the potential to set up feedback loops that enhance proliferation (Fig. 9). However, whereas HELLS is overexpressed and may contribute to tumor progression in prostate cancer [91], ATAD2 is apparently not significantly expressed in prostate cancer, but overexpressed in several other common cancers [92], similar to HELLS. ATAD2 and HELLS are rather intriguing proteins that appear to have several different roles in DNA transactions. They both function as co-activators for E2F transcription factors that stimulate G1 to S phase transitions, as outlined below. ATAD2 is an AAA-protein type ATPase (ATPase Associated with diverse cellular Activities) that is thought to be involved in chromatin remodeling and regulation of transcription [93]. Recruitment of ATAD2 to chromatin requires its bromodomain that binds to histone H3K14ac [94] and histone H4K5ac [95]. Importantly, H3K14ac was recently shown to facilitate nucleotide excision repair in yeast through stabilizing binding of a chromatin remodeling complex [96]. As mentioned, ATAD2 is overexpressed in a number of human cancers, but although ATAD2 is induced by estrogen and acts as a co-regulator for estrogen and androgen receptors, overexpression is not limited to hormone-dependent tumors [92,95,97–100]. Furthermore, ATAD2 overexpression appears to act as a driver of proliferation in cancer cells and is associated with poor prognosis [98,99]. Several observed functions of ATAD2 may be related to its direct interaction and function as co-activator for transcription factors that are involved in G1/S-transitions and proliferation, including E2F1, cyclin D_1, MYC, B-MYB, histone methyltransferase EZH2 and others [94,98–101]. It is reasonable to assume that the G1/S-regulation of ATAD2 itself contributes to the specific S phase functions of the gene products mentioned.

The G1/S regulated *HELLS* gene encodes an SNF2-related ATPase/helicase and was identified as a putative helicase with highest expression in T-cells in fetal mouse thymus [102], but is generally expressed in proliferating cells. Transcription factor FOXM1, reported to be G1/S regulated [103], is a central regulator of HELLS expression [104]. However, our laboratory (data not shown), as well as others, observed highest expression of FOXM1 in

G2/M/G1 [20,22,25], consistent with an additional important function of FOXM1 in regulation of several G2-specific genes as well [105,106]. HELLS promotes phosphorylation of H2AX to γH2AX and contributes to efficient repair of double-strand breaks in mouse cells [89]. HELLS contributes to de novo methylation of DNA by interaction with DNA methyltransferases and is involved in regulation of transcription [107–109]. It also has a role in methylation of histone H3K4 [110]. Furthermore, HELLS silences expression of the CDK4-inhibitor $p16^{INK4}$ by recruiting HDAC1 and possibly HDAC2 to the *p16^INK4* gene promoter, thereby increasing cell proliferation and delaying senescence [111]. The apparent role of HELLS in progression of prostate cancer may in part be explained by its function as a co-activator for transcription factor E2F3 [91]. In contrast, HELLS deficiency causes erythroleukemia in mice [108], and deletions are associated with acute myeloblastic- and acute myelogenic leukemia in humans [112]. In sum, the S phase regulated HELLS contributes to DSBR by promoting phosphorylation of H2AX to γH2AX and has complex epigenetic functions at the DNA and histone level. In addition, it acts as co-activator for transcription factor E2F3 that increases expression of several growth promoting genes. Depending on cell type it may both prevent and promote carcinogenesis.

Genes for RAD54B and RAD54L are also most highly expressed in G1/S or S phase. RAD54L (usually called RAD54) is a much-studied member of the SNF2 family of helicases, but may not be a functional helicase [113]. RAD54L interacts with RAD51, also a G1/S DNA repair and remodeling protein, to carry out the key reactions of homology search and DNA strand invasion [113]. In this process RAD51-ssDNA stimulates RAD54L-dependent chromatin remodeling in a homology-dependent manner [114]. RAD54B is another member of the SNF2 superfamily of helicases and is involved in DNA repair by homologous recombination. In the nucleoplasm, RAD54B co-localizes with RAD51 and BRCA1, both of which are also most highly expressed in G1/S. RAD54B is not an essential DNA repair protein, but it is synthetically lethal with loss of LIG4, required for NHEJ [115]. The mechanistic function of RAD54B in recombination is not clear.

Topoisomerase II encoded by *TOP2A* consistently has highest expression in the G2 phase. This is in accordance with earlier studies on TOP2A protein levels demonstrating highest levels during G2/M, although it is also expressed during the S phase [44]. Interestingly, subunits in the SWI/SNF complex, a much-studied remodeling complex, is required for binding of TOP2A to 12,000 genomic binding sites, indicating that TOP2A depends on the SWI/SNF complex to prevent entanglement of DNA at mitosis [116]. A major regulator of the *TOP2A* promoter is the transcription factor FOXM1, which itself peaks in S- and G2 phases of the cell cycle and binds to the *TOP2A* promoter and other S/G2-regulated genes [117].

3.12. DNA polymerases

We analyzed 16 DNA polymerase genes (including subunits) in the list of DNA repair genes. Seven of these are cell cycle regulated. DNA polα1, polδ1, polδ3, polε and polε2 are all expressed during G1/S- or S phase. DNA pol α, δ and ε are members of the family B polymerases, and the S phase dependent expression confirms their role in DNA replication. PolΘ and polσ are both most highly expressed in G2 phase. PolΘ is known to function in translesion synthesis in the FA pathway; it synthesizes DNA with low fidelity and is proposed to have a role in somatic hypermutation (SHM) of immunoglobulin genes [118]. DNA polβ is found to be independent of cell cycle phase, as previously reported [119]. This is consistent with its dual roles in short patch BER pathway [6] and its role in processing of DSBs during meiosis [120].

4. Conclusions and some concluding remarks

Whereas the core mechanistic steps in different DNA repair pathways are now reasonably well understood in principle, the regulation of DNA repair processes remains elusive. Expression of DNA repair genes is regulated at several levels, including post-translational modification [3,121,122]. Some aspects of cell cycle regulation of DNA repair genes was reviewed some years ago and our analysis are in general agreement with this paper [123]. Regulation of DNA repair and chromatin remodeling genes at the cell cycle level is the topic of the present paper. Reassuringly, the genome-wide cell cycle transcriptome studies largely confirm studies at the protein level, when information is available. As evident from our results and those of others, one DNA glycosylase is S phase regulated (e.g. *UNG*), another one (*TDG*) is G1-regulated, and two (SMUG1 and MBD4) are not cell cycle regulated, indicating non-redundant functions of these uracil-DNA glycosylases. Uracil-DNA glycosylase SMUG1 may serve as a general backup in genomic uracil-removal, particularly outside of S phase when UNG2 levels are lower. In addition it has an apparently unique role in removal of 5-hydroxymethyluracil from DNA. DNA glycosylases removing oxidized or alkylated bases either had insignificant cell cycle transcriptional profiles or were inconsistent between studies (NEIL3, which was detected as upregulated in late S phase, G2 and G1). However, NEIL1 was previously found to be upregulated and present in replication foci in S phase, indicating a possible role in pre-replicative repair [54].

We find that most of the FA genes are up-regulated during S phase, indicating that interstrand cross-links (ICLs) are detected and mainly repaired in S phase. The FA pathway may coordinate the activity of HR, MMR and NER proteins in ICL repair [124,125]. Several FA proteins are known to bind to DNA containing ICLs either directly or via nonerythroid α spectrin (also called SPTAN1) [126]. This protein also associates with ICLs in telomeres in the S phase and is required for their maintenance [127]. Some repair of ICLs also takes place outside of the S phase and in non-proliferating cells. This replication-independent repair pathway is thought to be initiated by RNA polymerase stalling; repair is slow and independent of the FA proteins, but may use some NER proteins and MMR proteins [18,128]. Proteins thought to be involved in this FA-independent ICL repair are mostly not cell cycle regulated.

DNA repair by HRR is most active during S/G2 phase when sister chromatids are available. In accordance with this, we found the highest expression of most HRR genes in the S phase. However, HMG20B (also called BRAF35) expression peaks in M/G1. HMG20B is a DNA-binding protein that interacts directly with BRCA2, which is required for HRR. BRCA2, in interaction with RAD51, is required for filament formation and strand invasion in HRR of double strand breaks [129]. Interestingly, the cell cycle pattern of HMG20B expression fits well with the observation that HMG20B and BRCA2 co-localized on mitotic chromosomes and that injection of antibodies to HMG20B caused G2-delay in the cell cycle [130]. These, and several observations not discussed here, indicate that HMG20B is a multi-functional protein involved in DSB repair and cell cycle regulation at the G2/M transition.

We find that several genes that are critical for HRR (e.g. *RAD51*, *RAD54L*, *BRCA1* and *BLM*) are expressed during G1/S transition and S phase, but are probably mostly used later in S phase when sister chromatids increasingly are available and HRR is at its maximum [131]. Repair by NHEJ is initiated by XRCC5 and XRCC6 which are not cell cycle regulated, consistent with NHEJ being active throughout the whole cell cycle. In the MRN complex, only MRE11 is cell cycle regulated, having induced expression during late S and G2 phase. Some reports show that the MRN complex is activated by protein phosphorylation which could explain why these genes are expressed independently of the cell cycle [132–134].

Chromatin remodeling proteins have important roles in genome maintenance processes, including DNA repair and DNA replication (reviewed in [135]) and at least for some types of repair recruitment of chromatin regulators is cell cycle regulated [136]. Most likely, many mechanisms of DNA repair, DNA replication and chromatin remodeling must be integrated and co-regulated. We find that transcripts from 8 chromatin remodeling genes are most highly expressed in S or G1/S in at least two data sets. In addition, 8 chromatin remodeling genes are translationally upregulated in S or G1/S. Many of these are known, or suspected, to have roles in DSBR by HRR or in restoration of nucleosome structure after HRR. Several of these apparently have roles in restoration of the nucleosome structure after MMR and NER. A requirement for chromatin remodeling has also been documented in BER, and appears to depend on the type of nucleosomes present in proximity of the repair patch and steps in the repair process [137,138]. In sum, DNA repair have cell cycle regulated expression more frequently than average genes, particularly in S phase. Chromatin remodeling genes, however, were not cell cycle regulated at a significantly higher level than expected.

Conflicts of interest

There are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dnarep.2015.03.007.

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