Chapter 5

Transcriptional Regulation of the Human Genes that Encode DNA Repair- and Mitochondrial Function-Associated Proteins

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http://dx.doi.org/10.5772/59588

1. Introduction

Mitochondria are thought to be evolved from primeval prokaryotes after symbiosis in anearobic cells, and they have their own circular DNAs (mtDNAs) and transcription/translation systems [1-3]. However, most of the genes (99%) that encode mitochondrial proteins and components of protein complexes are contained in nuclear genomes [3]. Previous researches revealed that mitochondria play important roles in the regulation of vital biological events, namely production of energy [4]. More importantly, recent studies showed that mitochondria exert signals to affect cell death [5], cellular senescence [6], and DNA repair systems [7]. These observations imply that mitochondria and nuclei are communicating each other to protect nuclear DNAs that encode 99% of mitochondrial proteins [8]. Furthermore, mitochondria also play roles in the responses to various stresses, including immunological reaction [9, 10].

Previously, we surveyed the human genomic DNA data-base and found that promoter regions of several DNA-repair-associated genes, including *ATM*, *BRCA1*, *FANCD2*, *PARG*, and *TP53*, which encode proteins that regulate mitochondrial functions, contain duplicated GGAA-motifs [11]. Moreover, numbers of DNA repair and mitochondrial function-associated genes are linked with partner genes by bidirectional promoter regions containing duplicated GGAA motifs [12]. These observations suggest that expression of the DNA repair and mitochondrial function associated factor-encoding genes are commonly regulated by GGAA-motif binding transcription factors (TFs).

In this chapter, we will focus on and discuss transcriptional mechanisms that regulate both DNA repair and mitochondrial functions. Not only DNA repair systems, but also several metabolic enzyme reactions that depend on an inner cellular NAD^+/NADH ratio, including TCA (Citrate/Krebs) cycle and poly (ADP-ribosyl)ation, are thought to be dys-regulated in cancer or tumor cells. We therefore, propose a novel cancer therapy by introducing GGAA-motif binding TFs or their expression vectors, activating both DNA repair and mitochondrial functions.

2. Relationships between DNA-repair, mitochondrial functions and Immune responses

Telomeres are the specific region of chromosomes that regulate cellular senescence and chromosomal integrity [13]. It has also been indicated that mitochondrial function is regulated by telomeres [6]. Several nuclear DNA-repair factors are suggested to play roles in the maintenance of mitochondrial DNAs (mtDNAs), and damaged mtDNAs in turn exert signals to regulate nuclear transcription [7]. Some of the DNA repair factors have been shown to localize in mitochondria. Furthermore, immune system has been suggested to be under the regulation of DNA repair [14]. Therefore, understanding the co-operation of the telomere-mitochondria-DNA repair-immune response might contribute to reveal molecular mechanism of cellular senescence, cancer and immunological diseases.

2.1. Characterization of the promoter regions of genes encoding enzymes that regulate human poly(ADP-ribose) metabolism

We have found duplicated GGAA-motifs in the bidirectional promoter of the human *PARG* and *TIM23B* genes that encode a poly(ADP-ribose) degrading enzyme and a mitochondrial inner membrane translocase 23B, respectively [11, 15, 16]. Isoforms of the PARG protein localize in the mitochondria [17]. PARP1 enzyme synthesizes poly(ADP-ribose)s on various target proteins, including p53 [18, 19] and PARP1 itself to regulate DNA-repair synthesis [20]. Interestingly, duplicated GGAA motifs are also contained in the promoter region of the human *PARP1* gene [21, 22]. PARP1 and PARP2 enzymes influence mitochondrial function and oxidative metabolism [23]. It has been shown that PARP1 protein localizes in mitochondria to maintain mitochondrial DNA integrity [24]. These observations imply that several DNA-repair factors localize in mitochondria, and that their gene expression may be partly controlled by the GGAA-motif binding protein factors.

2.2. DNA-repair factors and mitochondrial functions

It is widely known that damage on DNAs activates p53, which is transcribed from the *TP53* gene, allowing it to bind to 5′-regulatory elements and activate genes encoding cell cycle regulators, apoptosis- and autophagy-inducers [25, 26]. The p53 protein does not only act as a "guardian of the genome", but also serves as a metabolism regulator [27, 28]. Moreover, p53

has been reported to accumulate in mitochondria in response to stress [26]. One recent study revealed that mitochondrial disulfide relay causes translocation of p53 into mitochondria to facilitate its function for repairing oxidative damage to mitochondrial DNA [29]. However, overexpression of p53 in mitochondria would lead to depleted mitochondrial DNA abundance and a reduction in oxidative stress [30]. Oncogenic *RAS*-induced mitochondrial dysfunction, which causes oncogene induced senescence, is dependent on either p53 or RB [31]. As a tumor suppressor protein, RB plays a role in linking cell cycle exit with mitochondrial biogenesis [32]. RB is widely known to control cell cycle progression, maintenance of genome stability and apoptosis by interacting with the E2F family of TFs [33]. Recently, it was reported that mutation of E2F1 leads to mitochondrial defects in human cells [34].

Besides p53 and Rb, various DNA repair factors have been reported to localize in mitochondria or regulate their biological functions. For example, mutations of the *BRCA1* gene have become one of the hallmarks for diagnosis of breast cancer [35, 36]. BRCA1 protein, which plays a part in the repair synthesis of double-strand DNA breaks [37], is also involved in the mitochondrial genome maintenance to be trans-located into mitochondria especially when it is phosphorylated [38]. Deficiency of BRCA1, which interacts with FANCD2 protein, leads to phenotypes that resemble to Fanconi amaemia (FA) [39]. A number of additional DNA repair factors associate with FA proteins [40]. Recent study of transcripts from bone marrow cells revealed that FA patients have deficiencies in mitochondrial, redox and DNA repair pathways [41, 42]. Another DNA-repair deficient disease is Ataxia Telangiectasia (AT) that is caused by mutations on the *ATM* gene [43]. Recently, it was reported that lack of ATM causes reduced mitochondrial DNA integrity and mitochondrial dysfunction [44]. Moreover, it was suggested that mitochondria are required for the oxidative activation of ATM [45]. The duplicated GGAA-motifs are present in the 5′-upstream regions of the *BRCA1*, *FANCD2*, and *ATM*, which have bi-directional partner genes *NBR2*, *CIDECP*, and *NPAT*, respectively [11]. Although *BRCA2*, which encodes a tumor suppressor to repair double-strand DNA breaks [46, 47], has no bi-directional partner gene, the duplication of the GGAA-motif is present near its transcription start site (TSS) [11].

2.3. Apoptosis is executed by signals from mitochondria

Execution of apoptosis or programmed cell death is mediated by mitochondria in response to various stresses including DNA-damage and immunological stress signals [48, 49]. Previously, we reviewed the roles of the ETS family proteins on apoptosis, and found the GGAA-duplications in the 5′-regulatory regions of the human *PDCD1*, *DFFA*, *BCL2*, *FAS*, and *FASL* genes [50]. The findings imply that expression of the apoptosis regulating factor-encoding genes is under the control of the duplicated GGAA-motifs. Previous studies revealed that mitochondrial functions closely associate with apoptosis [5, 48, 51]. For instance, it is one of its characteristics that cytochrome c is released from mitochondria during induction of DNA-damage signals, and that apoptosis regulator proteins BAX and BCL2 localize in mitochondria [48]. Our *in silico* surveillance of the human genomic data base retrieved several interesting examples of duplicated GGAA-containing bidirectional promoters, including *ATG12*/*AP3S1*,

APOPT1/*BAG5*, and *HTRA2*/*AUP1* gene pairs [12]. The *ATG12* and *HTRA2* genes encode an autophagy protein that takes a part in the quality control after mitochondrial damage [52, 53] and a serine protease that is localized in mitochondria [54], respectively. Importantly, with assistance of tumor suppressors, such as p53, RB1 and BRCA1, ATG12 and HTRA2 may contribute to determine cell fate between DNA-repair and cell death after excess cellular stresses.

2.4. Identification of duplicated GGAA (TTCC) motifs in the 5′-upstream of the human genes encoding DNA repair factors and apoptosis regulators

We have reported that duplications of the GGAA-motif are found in the 5′-regulatory regions of the human *TP53* and *RB1* genes [11]. Moreover, we have found the DNA sequence 5′-CAATA**GGAA**CCGCCGCCGTTG**TTCC**CGTC-3′ near the TSS of the human *E2F1* gene. These lines of evidences imply that tumors could be generated from mitochondrial dysfunctions when p53 and RB proteins lose their intrinsic biological functions as tumor suppressors, and that expression of their encoding genes are under the control of GGAA-motif binding TFs.

We have also identified GGAA-motif duplications in the 5′-upstream of the *APEX1* gene, which has a bidirectional partner gene *OSGEP* [11]. The *APEX1* encodes apurinic/apyrimidinic endonuclease 1 (APE1) that regulates both base excision repair and mitochondrial DNA-repair systems [7, 55]. It is noteworthy that APE1 interacts with XRCC1, which is recruited to the poly(ADP-ribosyl)ated site [56]. APE1 does not only function as a regulator of the base excision repair system, but also as a redox regulator [57]. The GGAA-duplication is contained in the regulatory region of the head-head configured *ACO2*/*PHF5A* genes [12]. The *ACO2* encodes aconitase that functions in the TCA cycle to produce citrate and isocitrate and also serves as a mitochondrial redox-sensor [58]. More importantly, a recent study revealed that aconitase and mitochondrial base excision repair enzyme OGG1 (8-oxoguanine DNA glycosylase) cooperatively preserve mitochondrial DNA integrity [59]. Additionally, it has been shown that Cockayne syndrome (CS) proteins CSA and CSB, which play roles in nucleotide excision repair, accumulate in mitochondria upon oxidative stress [60]. A putative ETS1 binding motif is located, though no obvious duplication of the GGAA-motif is present near TSS of the *ERCC8* (*CSA*) gene. Interestingly, it has a bidirectional partner *NDUFAF2* that encodes one of the components of the NADH dehydrogenase (ubiquinone) [12]. The observation implies that not only GGAA-motif-duplication, but also another *cis*-element may take part in supporting transcription from a bi-directional promoter.

Collectively, our *in silico* analysis of the 5′-upstream regions of human genes suggested that transcription of a large numbers of DNA-repair/apoptosis/mitochondrial function associated genes could be regulated by duplicated GGAA-motif-containing promoters.

2.5. DNA-repair and immune responses

It should be noted that duplicated GGAA (TTCC) motifs are frequently contained in numbers of 5′-upstream region of the human interferon (IFN) stimulated genes (ISGs) [61]. BRCA1 has been reported to regulate IFN-gamma signaling by inducing *IRF7* gene expression [62].

MRE11, which is a double-stranded DNA break sensor with Rad50, is required for activation of stimulator of IFN genes, STING [63]. These lines of evidences imply that response to IFN should be co-regulated in accordance with DNA repair system when damage was introduced in chromosomal DNAs. Conversely, IFN signaling affects expression of genes encoding DNA repair factors. Recent studies revealed that immune system is closely associated with DNA-repair system. It has been reported that transcription of the *FANCF* gene is up-regulated by IRF8 during differentiation of myeloid cells [64]. Moreover, IRF1 has been shown to regulate *BRIP1* (*FANCJ*) gene expression [65]. IL-4 decreases DNA damage in murine and human glioblastoma cells when PARP-dependent DNA-repair is required [66]. Over expression of the IFN-related genes are caused by treatment with DNA-damaging agents and following ionizing radiation [67]. Interestingly, this over expression is enhanced in the BRCA2 knockout cells.

Integration of viruses into chromosomes might be damage on DNAs because exogenous DNAs will cause disruption of genes or enhancer insertions. Therefore, DNA repair system should be immediately evoked upon viral infection. Hence, immune sensing is primarily required to anti-viral immunity. It was indicated that oxidized base 8-hydroxyguanosine (8-OHG) potentiates cytosolic immune recognition by decreasing its susceptibility to TREX1-mediated degradation [68]. TREX1, which is also known as DNase III, is a 3' exonuclease that is thought to play an important role in HIV-1 DNA sensing and viral immune evasion [69]. Interestingly, *TP53* gene expression is induced by type-I IFN signaling in $CD4^+$ T cells upon infection of HIV-1 [70]. Importantly, the concept has been postulated that DNA damage response affects innate immune sensors that drive metabolism, apoptosis, cancer, and aging [14].

Overall, the DNA repair system, including DNA damage sensing, and IFN response are thought to depend on and regulate each other. Previously, we identified duplicated GGAA (TTCC) motifs in a number of DNA repair associated genes, including *TP53*, *RB1*, and *BRCA1* [11]. In order to examine if GGAA (TTCC) duplication is a common feature of the 5'-upstream region of the DNA repair associated genes, we proceeded to re-survey of the data base of the human genomic DNA.

3. Comprehensive analysis of the DNA repair-associated gene promoter regions

First, we retrieved 568 gene IDs from NCBI_GENE data base (http://www.ncbi.nlm.nih.gov/gene/) with a key word "DNA repair" on July 20, 2014. Then, we accessed to their individual sequence data and searched GGAA or TTCC motifs within a region between approximately 540 nucleotides upstream and 90 nucleotides downstream from the putative TSSs. At least one duplicated GGAA (TTCC) motif is contained in the 630 nucleotide region of 358 different genes (Table 1). Our defined GGAA (TTCC) duplications, with no more than ten nucleotide distance between GGAA (TTCC) sequence pairs, are not found in the remaining 210 genes (not shown). These genes, whose putative promoter regions contain duplicated GGAA motifs, could be classified into several groups according to the biological functions of the encoded proteins.

Gene-Partner gene	Sequence
ABL1	CGGCA**GGAA**ATTTGTT**GGAA**GATGA, GTGAC**TTCC**ACA**GGAA**AAGTT
ACTL6A	CTACC**TTCC**CCTACCCGGG**TTCC**CGCCG, GCTTC**TTCC**AGCC**TTCC**TCCTT, TCGCT**TTCC**TCT**TTCC**CGCCC
ADH5-LOC100506113	TGAAA**TTCC**CG**TTCC**CTCACC, CACGG**GGAA**GCCCT**TTCC**CGACA
ADPRHL2(ARH3)-TEKT2	GATGG**GGAA**CACTA**TTCC**TCCGA, CGGAC**GGAA**GTAG**GGAA**ACTGT
AKAP9	GAGTG**GGAA**CCAGTGGAG**GGAA**GAGGG, CCACC**GGAA**CTT**TTCC**GTTGG
ALKBH1-SLIRP	GCCCC**GGAA**AAAAT**TTCC**GGATCC**GGAA**CACGA, CTTTC**GGAA**ACTT**TTCC**GCTTC
ALKBH4-LRWD1	CGACC**GGAAGGAA**GC**GGAA**CCCAG
ALKBH6-LOC101927572	AGACG**GGAAA**G**GAA**GTGC**TTCC**TTCAG
ALPK2	AGTTT**TTCC**T**TTCC**TAAGG, TCTTC**TTCC**AGAAC**TTCC**CCGGGCAT**GGAA**T**TTCC**CCTCTTA**GGAA**GAGAT
ANKRD26	GACAT**GGAA**GG**GGAA**TAAAC, AGATT**GGAA**ACCGCGGAGT**TTCC**TTTGG
APC	AGGAT**TTCC**C**GGAA**GAGGT
APEX1-OSGEP	CAGCT**TTCC**GGAGCGCAGA**GGAA**GCTGG, CACTG**GGAA**AGACACCGC**GGAA**CTCCC, CCGTT**TTCC**TATCTCT**TTCC**CGTGG
APITD1	CGCAG**TTCC**TG**TTCC**ACTCG
APOBEC3B	CACAC**TTCCTTCC**CCACT, GGAGG**TTCC**TCTGCCAGCG**GGAA**GGGTCCGG**GGAA**AACCA
APOBEC3G	AAGCA**GGAAGGAA**AGAGC
AR	AGGTA**TTCC**TATCGTCCTT**TTCC**TCCCTC, GGGAG**GGAA**AAGGAGGTG**GGAA**GGCAAG
ASCC3	TAATA**GGAA**TTAT**TTCC**TCCAC
ASF1A	AAAGT**TTCC**GAGTCCA**TTCC**GGGAG
ASTE1-NEK11	ATCAC**GGAA**CTGTAC**TTCC**CAGAG, GAGAC**TTCC**GA**TTCC**CGCTC
ATF2	TGCTG**GGAA**GTGAC**GGAA**ACGGA
ATF3	TACTA**GGAA**A**GGAA**TCTGT
ATF4	TCGCC**GGAA**AACGACCT**TTCC**CCGCC
ATM-NPAT	AAAGC**TTCC**CTACCAAG**GGAA**AACCT, CAGCA**GGAA**CCACAATAA**GGAA**CAAGA, CCTTC**GGAA**CTGTCGTCAC**TTCC**GTCCT
ATR	CGGTG**GGAA**CGTGA**GGAA**CTTTT, ACGGC**TTCC**CGGC**TTCC**CCCGG
ATRIP	CATCA**TTCC**TCCTTGGACT**TTCC**TCCTC
ATRX	TTGGT**TTCC**TCATCT**GGAA**AATGT

Gene-Partner gene	Sequence
AURKB	CTGGG**GGAA**TTTGG**GGAA**ACT**TTCC**TAAACT**GGAA**GCCAA, TCTCA**TTCC**GCCTC**TTCC**ATTGGG**TTCC**CATGA
BACH2	TGCCC**TTCC**G**GGAA**AACGC
BARD1-LOC101928103	GCAGC**TTCC**CTGTGGT**TTCC**CGAGGC**TTCC**TTGC**TTCC**CGCTC
BCCIP-UROS	CTACG**GGAA**GGGGAGG**GGAA**GCTTT, GAGGGT**GGAA**AGC**GGAA**GAAAA, GCCGT**GGAA**AGTGGGG**TTCC**GCAGC, GACGA**GGAA**GA**GGAA**AAAGA
BCL2	TTTTA**GGAA**AAGAG**GGAA**AAAAT
BCR-BCRP8	AAGTG**TTCC**TG**TTCC**AGGAC
BLM	CCGGG**TTCC**AGCTGCCTAC**TTCC**TTTAA, TCGGC**TTCC**CCA**GGAA**GCAGCCAATC**GGAA**TAGGCAAGC**TTCC**GGCG**GGAA**GTG AG
BRCA1-NBR2	ATGCT**GGAA**ATAATTAT**TTCC**CTCCA, AATTC**TTCC**TC**TTCC**GTCTCT**TTCC**TTTTA, TTGGT**TTCC**GTGGCAAC**GGAA**AAGCGCG**GGAA**TTACA
BRCA2(FANCD1)	GACAA**GGAA**T**TTCC**TTTCG
BRE-RBKS	TCTTC**TTCC**T**GGAA**TAGTC, GCTGA**GGAAGGAA**CTGTC
BRIP1 (FANCJ)	GATAC**TTCC**T**TTCC**GCTGG, GAGAC**TTCC**AGT**TTCC**AA**GGAA**TTTGC
BTG2-LINC01136	CCACG**GGAA**G**GGAA**CCGAC
C17orf70	CCCGC**TTCC**CCACCCTGG**GGAA**CCCGT
C19orf60	CTTGG**TTCC**CCTTTC**TTCC**TTCTG
CAGE1-RIOK1	GCGAT**GGAA**A**GGAA**CGGCT
CCNF	GCGGC**GGAA**G**GGAA**GGCCG
CCNO	CTGGC**GGAAGGAA**GGGCA
CDC20	CAAGC**TTCC**CAA**TTCC**GTCCC, TCTCC**TTCC**CCTTCTA**GGAA**CGGCT, AGACT**TTCC**CC**GGAA**GGCCC
CDC25	GCCTC**TTCC**CACTAGG**TTCC**ATCAT, GGAGG**GGAA**AGAG**GGAA**GGAGG
CDK1	TTTTT**GGAA**TCT**GGAA**TATTA**GGAA**TCAAC
CDK2-PMEL	CGAGA**TTCC**CGGC**TTCC**TGGT**TTCC**AAAGG, GCCAG**GGAA**ACGCG**GGAA**GCAGG
CDK5-SLC4A2	CCCAT**TTCC**GCTGCATTCT**GGAA**CGCGT, AAACT**GGAA**AAGATTGG**GGAA**GGTAAT**GGAA**TCTCG
CDK5RAP2	GGTTA**GGAA**CTTTGAGGA**TTCC**TGAGT, CTCGT**TTCC**GTA**GGAA**GAAGCGCCG**GGAA**AGATG
CDK6-LOC101927497	TGTGT**TTCC**TT**GGAA**TCGGC
CDKN1A(p21)	CATTG**TTCC**CAGCAC**TTCC**TCTCCC**TTCC**TAGGC, CCTGC**TTCC**CA**GGAA**CATGC

Gene-Partner gene	Sequence
CDKN2A(p16)-CDKN2AAS1	AGCCA**GGAA**TAAAATAAGG**GGAA**TAGGG
CEP63-ANAPC13	AAGCG**GGAA**AGCCTTG**TTCC**TTGCT, CGATG**GGAA**TAGGG**GGAA**GTCCG, TCGCT**TTCC**TCGGA**TTCC**CGGAT
CFL1	GAGAT**TTCC**TTGTACCT**TTCC**CCTGTGCCTT**TTCC**TCCTA, AGCGG**TTCC**TG**GGAA**ATTGG
CHAF1A	TGGGA**GGAA**T**GGAA**GTCAC
CHAF1B	ATAAA**TTCC**GGCCGGGA**TTCC**GACCC
CHD1L-PRKAB2	GTGGG**TTCC**TTATAG**GGAA**TAAGA
CHEK1	TTTTT**TTCC**TAC**GGAA**TCATG, TCGCC**TTCC**CAAAGTGCT**GGAA**TTACA, CTTAT**TTCC**ATTT**TTCC**TATTT
CINP-TECPR2	ATCGG **TTCC**T**TTCC**CGGGG
CLOCK	CGGCA**GGAA**GCTCTTC**TTCC**TCCTC
CLSPN	CCACG**GGAA**CCTT**GGAATTCC**TCTAA, GCCCA**GGAA**CCGT**TTCC**CAGCTCAC**TTCC**CCCCG
CLU	CTGAT**TTCC**TAACTG**GGAA**GGCTC, GGCTC**TTCC**CTACT**GGAA**GCGCC
COCH	AAGTA**GGAA**CTCT**TTCC**ACGAG
COL6A6	GTCCG**TTCC**ACGG**TTCC**GAGGT, TGCAT**GGAA**GT**TTCC**CCAAG
COPS5	CCTTC**TTCC**GGTGC**GGAA**GACTA
CPT2	GAGTT**GGAAGGAA**TCTTG, TGACA**GGAA**GCCTC**TTCC**AATAG, AACAC**GGAA**GAC**TTCC**TAGAG, GGGGA**TTCC**GCTC**GGAA**GGGGC, CAGCG**GGAA**ACTCCAGGT**TTCC**AACTC
CRY1	AAAAA**TTCC**A**GGAA**GTCCA**GGAA**TGCCT, CTGAA**GGAA**ACCGGACAAT**TTCC**AGGCC
CSNK1D	CGCGA**GGAA**CTCACCTGGC**TTCC**TCGAC
CSNK1E	TCCCA**GGAA**CTGTGC**TTCC**GGGAT
CUL4A	ATCCA**TTCC**CTATAT**TTCC**TATCC
DCK	ACTCC**GGAA**CCTC**TTCC**CGCGC
DCLRE1A-NHLRC2	CAGCG**GGAA**CTTG**TTCC**CGCCA
DCLRE1B	TCCAG**TTCC**AGCCTTAA**TTCC**CCCTC
DCLRE1C-MEIG1	TAAAC**GGAA**GAG**GGAA**TTAATAG**TTCC**TGAAT, AAGCA**GGAA**GC**GGAA**CGAAG, TCGAT**TTCC**C**TTCC**CGCGA
DDB1-DAK	AGTCC**TTCC**CG**TTCC**CAAAGGA**GGAA**CAGCCC

Gene-Partner gene	Sequence
DDX1	GAGGA**TTCC**TCATTTACT**TTCC**CCATC
DDX11-DDX11AS1	GAGCG**GGAA**AACA**TTCCGGAA**GTGGA
DEK	ATCTT**TTCC**A**GGAA**GCGACCGT**GGAA**ACAAT, CGTCC**TTCC**G**TTCC**GCGCT, CCGCA**TTCC**CGCTCTCC**TTCC**CGAAC
DHFR-MSH3	GGCTC**TTCC**CACC**TTCC**CCTTC
DNTT	GATCT**GGAA**AACATAG**TTCC**AAGTG, GATGC**TTCC**CTACC**TTCC**TCACG
EGF	GGGAT**TTCC**CTTTGATTT**GGAA**AGAAT, CCTGCT**TTCC**TGTGTGGA**GGAA**TTGCC, TAGCT**GGAA**CT**TTCC**ATCAGTTC**TTCC**TTTCTTT**TTCC**TCTCT
EGFR	AGAAG**GGAA**AGGG**GGAA**GGGGA, TGCTG**GGAA**CGCCCCTCTC**GGAA**ATTAA
EGR1	AGGGC**TTCC**TGC**TTCC**CATAT
EIF2AK3	TTGTA**GGAA**AGGTA**TTCC**G**GGAA**CTGAT, CACCAG**GGAA**AGTCCACC**TTCC**CCAAC
EIF3A	GCTCC**TTCC**T**TTCC**GTCTC
EME2-MRPL34	CGGCC**GGAA**GTCACC**GGAA**GAGGC, CGGCC**GGAA**GCGA**GGAA**GAGGT
ENDOV-LOC100294362	GGGTG**GGAA**GTGCGGCCCG**GGAA**AGCGC, GTCGC**TTCCGGAA**GTGACGTGC**GGAA**GGGGT, CCAGT**TTCC**GGCGC**GGAA**GCGGA
ENG	TCTAA**GGAA**GCGCAT**TTCC**TGCCT
EPC1	TTTTT**TTCC**CAA**GGAA**TTAAA
EPC2	GGAGG**GGAA**GGGAGA**GGAA**GGAGG
ERBB2-PGAP3	GAAGC**TTCC**AC**TTCC**GGAGTAACC**GGAA**G**TTCC**TGTGT
ERCC1	AATTC**GGAA**TT**TTCC**GAGAA
ERCC2(XPD)	GCTCT**TTCC**C**TTCC**ATGTT
ERCC3(XPB)	GGAGC**TTCC**GGATTGAGCC**GGAA**GTCCC
ERCC4(FANCQ)	CTTAC**TTCC**CC**TTCC**CTTGC
ERCC6L2-LINC00476	CAGAG**GGAA**GAGACATCG**GGAA**GATTG
ERN1	GTTCA**TTCC**AAGC**GGAA**GTGAT, TGAGG**GGAATTCC**TGAGGGCAA**GGAA**AA**GGAA**GAAAG
EWSR1-RHBDD3	CGGAC**GGAA**CCA**TTCC**AAACA
EYA1	CTTTT**GGAA**GAACCGG**TTCC**TCAGC
EYA3	ATGTC**TTCC**AAAAC**TTCC**CACTC, CTTAC**TTCC**GG**TTCC**TAGCG
EYA4	GAGAG**TTCC**AG GCAA**TTCC**GGGGG, GGCCG**TTCC**CGGC**TTCC**GCGCAA AAC**TTCC**ATCCT, GAGGG**GGAA**AGAGCTGCG**GGAA**AAGCC

Gene-Partner gene	Sequence
FANCA	AGTCT**GGAATTCC**TGGGC, AGTCA**TTCC**CGGCA**GGAA**CCACG
FANCB-MOSPD2	GAGTC**TTCCCTTCC**CAGGA, GAGAG**GGAAGGAA**GCGGG
FANCC	TCGTC**GGAA**TT**TTCC**CGCGA, CCGCG**GGAA**AA**TTCC**AAAAA
FANCD2-CIDECP	CGGCC**TTCC**AC**TTCC**GGCGC**GGAA**GTTGG
FANCE	CCTCC**TTCC**CT**TTCC**GACAGCGCG**GGAA**CGGCT
FANCF	GATAT**TTCC**AAAGCGAAA**GGAA**GCGCG, CGTGG**TTCCGGAA**ATTCT
FANCG	TCGGT**GGAA**GCG**GGAA**CCCAG
FANCI	CTGCC**TTCC**AGGCTT**TTCCA**GTGC
FANCL	TTCAT**TTCC**GCCCGC**GGAA**TCCTC
FANCM	TCATT**GGAA**AC**GGAA**CTTAA, AATCA**TTCC**CAAC**GGAA**ACTCA
FBXO6	CATAA**GGAAGGAA**CTAGT
FEN1-TMEM258	GGGGC**TTCC**CCC**TTCC**CCACC, CAACC**GGAA**AA**G** **GAA**GTGCC
FGF10	AATTC**GGAA**AGCG**GGAA**GATAC
FNDC4	GAGGT**GGAATTCC**TC**TTCC**CAACT, GGCTC**TTCC**ACGCGGGGA**GGAA**GGGGA
FOXM1	ACGAT**TTCC**CCCAGTGA**GGAA**ATCAA
FOXO3	CTCGT**GGAA**GGGAGGAGGA**GGAA**TGT**GGAA**GGTGG
FUS	CCACA**GGAA**TCTCGG**TTCC**ACCCC
GLB1	TGCAG**TTCC**AAAGGGTCCC**TTCC**CAG**GGAA**GACGC
GSTP1	GCAAT**TTCC**T**TTCC**TCTAA, CTTAG**GGAA**T**TTCC**CCCCG, ACCTG**GGAA**AGAG**GGAA**AGGC**TTCC**CCGGC
GTF2H1-HPS5	TCGCG**TTCC**TCCCC**TTCC**TTGCT, GGGAG**GGAA**CTAGC**GGAA**GGTGT
GTF2H2	GTGAA**TTCC**AGCT**GGAA**CACCGTCCCT**TTCC**GCGCC, GCGGC**GGAA**TGAC**TTCC**GGGGC
GTF2H3-EIF2B1	CCCAC**TTCC**GGCGCAC**TTCC**GTACCCCTC**TTCC**GGCGC
GZMA	AGTGG**GGAAGGAA**AATCC
H2AFX	TGGTC**TTCC**GCTTCTGGT**TTCC**GATTG
HERC2	GGTGT**TTCC**TTCTTCGA**TTCC**CTGCA, GTGGC**GGAA**ATCCCGCC**TTCC**GGCGC
HELQ-MRPS18C	CATGG**TTCC**GCGTTTC**TTCC**AC**TTCC**TTTCG**TTCC**AAATCG**TTCC**GAAAGGCCCC**TT** **CC**GCTGCTC**TTCC**CCTGT
HINFP	CACTG**TTCC**CGCCCC**TTCC**GTGTT
HLTF-HLTFAS1	ATAAA**GGAA**GGTCGT**TTCC**CTCCG

Gene-Partner gene	Sequence
HMGB2	GGGCT**TTCCTTCC**CGAGC
HNRNPC	CAATA**GGAA**GATTCTCA**GGAA**TGGGG
HSPA1A-HSPA1L	ACCCT**GGAA**TA**TTCC**CGACC
HSD17B6-PRIM1	CCACA**GGAA**TTGGCG**GGAA**CAGCA, CGCCG**GGAA**TTGTAG**TTCC**CACTT, GTCCA**TTCC**A**GGAA**GAGGA
HTATIP2	AGAAA**GGAA**TCAAA**GGAA**TCCTG, GTGAG**GGAA**AACGCG**GGAA**GAGGG, GCAGA**TTCC**AAACTTA**GGAA**GGGTC
HUS1B	GGAGT**GGAA**AC**GGAA**GCATT
HUWE1	TCATG**TTCC**C**TTCC**GCGGC**TTCC**ACCGT
IER3	TCGTC**GGAA**T**TTCC**AGCCC
IGF1	AAATG**TTCC**CCCAGCTGT**TTCC**TGTCT
IGF1R	TGAGC**GGAA**AAAAAAAG**GGAA**AAAAC
IGFBP3	GCCGC**TTCC**TGCCTGGA**TTCC**ACAGC
IGHMBP2-MRPL21	CGGCC**GGAA**AC**GGAA**ACGAC
IL18	TGGGA**GGAA**GG**GGAA**GTCCT, TCGAC**TTCC**ATTGCCCTA**GGAA**AGAGC
INO80B	GGACC**GGAA**CGTTCGTT**GGAA**GGATC, AGTTT**TTCC**GCGGGGC**GGAA**AAGGC
INO80C	ACCTT**TTCC**GCGTG**GGAA**GGCAG
INO80E-HIRIP3	AGTCA**GGAA**CGGCGCT**TTCC**AGCGT, ATACC**GGAA**TCTGAAGC**GGAA**GCTCAAG**TTCC**TCATC
IPO4	GGGCA**TTCCTTCC**CCAGA, GCCCT**TTCC**TCC**GGAA**GTGGG
IPPK	AGGCC**GGAA**GCTTCTC**TTCC**GGCTC, CCGCG**TTCCGGAA**ATGAG
IRS1	TAAAT**TTCC**TGGG**GGAA**ACAGC
JMY	GGGCT**TTCC**TCAGACACC**TTCC**TTTCA, CTCAG**TTCC**TCCGCCTTAG**TTCC**TCTT**TTCC**CGGGT, TGCGC**GGAAGGAA**GGAGA
KAT5	AGCTA**GGAA**TC**TTCC**CTGAG
KDM4A	GCAGC**TTCC**C**TTCC**CTGTT
KIAA0101-TRIP4	CCATC**TTCC**CCAGCC**GGAA**CCAGC,
KIF2C	GAAGT**TTCC**CAGTTTTCG**GGAA**CCCCG, GCGTA**GGAA**GATGGTTG**GGAA**CTGCG
KIF13B	TGGCA**GGAA**ATGAGCA**GGAA**GAGGT
KIF22	GACTG**GGAA**CC**GGAA**CCGTG
KIN-ATP5C1	CCCGG**TTCC**GT**TTCC**GGCTG
KLF8	CTCCG**TTCC**TTTTAGC**TTCC**TCCCT

Gene-Partner gene	Sequence
KRAS	CCCTC**TTCC**CTC**TTCC**CACAC
LCT	ACATT**TTCC**GGG**TTCC**TCTGC
LMNA-MEX3A	TTTCT**TTCC**ATTA**TTCC**AGATA, GTGGT**GGAAGGAA**AAGAG
LIG1-C19orf68	GGCGC**TTCC**ACCGA**TTCC**TCCTCT**TTCC**CTGCC
LRRCC1	AATGT**TTCCAGGAA**CAAGA, TTTTC**TTCC**TCATACAG**GGAA**GTGAC, AGGCG**GGAAAGTTCC**CGGCT
MAD2L1	TCTCG**GGAA**AAGCTGCG**TTCC**CACAC
MAD2L2-DRAXIN	GGACT**GGAAGGAA**GGGGG
MCM8-TRMT6	GCCGC**TTCC**GCT**TTCC**GGCCC, ACCGC**TTCCGGAA**GCCTCTCGGC**TTCC**GTCTG, CTTCT**GGAA**GCTGCGGTGG**GGAAAA**CTGAGT**TTCC**CGAGC
MCRS1	TCGTG**GGAA**TTT**GGAA**GTCGA, AACTA**GGAA**AGCCTTTACT**TTCC**GCTAT
MDC1	ACGTA**TTCC**CA**GGAA**GAAAG, CAAAA**GGAA**ATGAAA**TTCC**AATGC
MGRN1	CGCTT**GGAA**CGCAGAG**GGAA**GGACC, GTTGG**TTCCTTCC**CTCTG, TCCTG**GGAA**AGATAG**TTCC**CAGACGGGC**TTCC**CGCGCTGC**TTCC**CGGCG
MIR96	ACGTC**GGAA**ACAGGCTGC**TTCC**AAGGG
MMS22L	GTGCT**TTCC**AAGTT**TTCC**ATATC
MNAT1	TCATG**GGAA**TGT**TTCC**AGACA, AAGAT**GGAA**TTTATC**TTCC**TAATT, CCGGG**GGAA**CTGACTGCC**GGAA**CGTTT
MORF4L2	ATTTT**TTCC**TA**GGAA**TGAAC
MPG	GGCTG**TTCC**CACA**GGAA**GGAGA
MPLKIP-SUGCT	GTAGC**GGAA**GCAGC**TTCC**GG**GGAA**CCCCG
MRE11A-ANKRD49	GCAGG**TTCC**CAGGC**GGAA**GCCCA
MSH3-DHFR	GATTC**TTCC**AGTCTACG**GGAA**GCCTG
MSH6	CGCTG**TTCC**CGC**TTCC**GCTCC
MSL1	CCGCT**TTCC**CCTTC**TTCC**CGCGG
MYB	GTGCG**GGAA**T**TTCC**CCCCA
MYO5A	CCCTA**GGAA**TGCTT**GGAA**GGACG
NABP2-RNF41	TCCCG**GGAAGGAAGGAA**AGG**GGAA**GGAGG**GGAA**AGAAG
NBN(NBS1)	GGTTG**GGAA**GCTACT**GGAA**TTAGG, CAGGT**GGAA**GT**GGAAAGGAA**GGGTA, CTAGA**TTCC**AAA**GGAA**TACCT, TGCTG**TTCC**TT**TTCC**AACCA
NCOR2	GGCGC**TTCC**CCCCTCC**TTCC**TCCTC
NDNL2	TGCAC**GGAA**AACGCTG**TTCC**TTTTGG
NEIL1	GGCGG**TTCCTTCC**GCCGG

Gene-Partner gene	Sequence
NEIL2	CCACT**TTCC**AG**GGAA**TGAGC
NES	CCTGG**GGAA**GCA**GGAA**CAGAG
NFRKB(INO80G)	GGACG**GGAA**GGA**GGAA**TGAA**GGAA**CTCGGAAGCACA
NIPBL-LOC646719	GTGGC**GGAA**GTGGAGTGG**GGAA**GAGGG
NLRP11-NLRP4	CGGCT**GGAA**GCG**GGAA**GAAAA, GGAGG**TTCC**TATTGAGAA**TTCC**CAGGG
NONO	TCCCC**TTCC**TCTCCCTCT**TTCC**ACT**TTCC**TCTCC
NPAS2	GCAGA**TTCC**TTG**TTCC**CCCCG
NPM1	CATCT**TTCCTTCC**TAACA
NR2C2	CGCTG**GGAA**GA**GGAA**GAAGA
NSMCE1	CTCAG**TTCC**ACAGATGG**GGAA**ACTGA, CAAGT**GGAA**GCCCC**TTCC**CATTA
NSMCE4A	CGAAC**TTCC**GCCG**TTCC**GAAGT
NUDT1-FTSJ2	CCCGG**GGAA**CTGCGACCC**GGAA**TCCTG
NUPR1	ATCCC**TTCC**CCCTCC**TTCC**TCACG
OFD1	TAAAT**GGAA**TCACTAATGA**GGAA**AGGCA
OTUB2	TACCC**TTCC**TGGA**TTCC**AGAAA
PALB2(FANCN)-DCTN5	AGAGA**TTCC**GGCTAC**TTCC**GGCCG
PARG-TIMM23B	GCCGC**TTCC**CCCGCCTCC**TTCC**ATGGT, TGACA**TTCC**GGGCGCCGG**TTCC**CGTTA, GCCCC**GGAA**GCC**GGAA**GCGCC, CAGCT**TTCC**GGTGGTG**GGAA**AGTGA
PARP1	GCGGG**TTCC**GTGGGCG**TTCC**CGCGG
PARP2-RPPH1	CCCCC**TTCC**CCC**TTCC**AGCTC
PARP4	CCTGT**TTCC**ACGAACT**TTCC**CGAAA, CCCGA**TTCC**GGGCGCG**TTCC**GGCTA
PARPBP-NUP37	AAGTG**GGAAGGAA**GAACTCCTG**GGAA**TAGAG
PDE4DIP	TCAAG**GGAA**AATTGAAA**GGAA**AAGATTTTA**GGAA**AGAGA,
PIWIL2-LOC100507071	CACAG**GGAA**CCTGCT**GGAA**AGGAC
PMS2-AIMP2	TGGAG**GGAA**CT**TTCC**CAGTC, CGGCA**TTCC**AACCTCCCT**GGAA**ATGGGG**GGAA**CATGG
PNKP	AGATG**GGAA**AAAAATC**TTCC**TCCCT, GTCAT**TTCC**GTCCGCCGA**GGAA**CCGAC
POLA1	TCGCT**TTCC**CGGCTCTGG**GGAA**AACGA, CTCCT**TTCC**G**GGAA**AATGG, TGGCC**TTCC**GGCC**GGAA**GTCCG
POLB	CCCGT**TTCC**CCTTCTAG**GGAA**AGGA**TTCC**AGATA, AGGTC**TTCC**CATA**GGAA**GGCCC
POLD1	GGCGG**GGAA**CAGC**GGAA**GTGAG

Gene-Partner gene	Sequence
POLD3	CCTCT**GGAA**AAACC**TTCC**CTAAT
POLD4	GCCTA**GGAAGGGAA**AACG**GGAA**GTGAG
POLG	CTTCG**TTCC**TGAGGGA**GGAA**TAAAC
POLH-XPO5	AGCCC**TTCC**ATT**TTCCTTCC**AGTAG
POLI	CAGGC**GGAA**GCGGCC**GGAA**GTAGC
POLL	AACCG**TTCC**AGAGGGTCAC**TTCC**GGCTGACTC**GGAA**GCTAT
POLM	GGGGC**TTCCTTCC**GTCTC
POLQ	CCCAA**TTCC**TCATTACATA**TTCC**TCACA
POLR2A-ZBTB4	GGGCG**GGAAAGGAA**GGGGC, ACCTT**TTCC**TT**TTCC**CTTCT, AAAAT**TTCC**GGTAAG**GGAA**AGAAG, CTTAT**TTCC**CCGCCTCC**TTCC**CTCCCCCACC**TTCC**CCTCC
POLR2B	TTCTG**GGAA**CGTCGGAGAC**GGAA**GTTAC
POLR2F-C22orf23	CTCCC**GGAA**GTGAT**TTCC**TCTGG, GCCGA**GGAAGGGAA**GGGCG
POLR2G	AGTGT**TTCC**GGTGGA**TTCC**CAGGG
POLR2I	CCCCC**TTCCGGGAA**CCCCC, GTCCC**TTCC**CCACCGCCA**GGAA**GAGGG
PPM1D	CCTTT**GGAA**GGGAGGT**TTCC**CGCCA
PPP1R15A	CTTAC**TTCC**AC**TTCC**CACCC
PPP5C	AGAGA**GGAAGGGA**AGATTT
PRKDC(DNA-PK$_{CS}$)-MCM4	ATCGA**GGAA**CAAACTT**GGAA**CTCTT, CGTTT**TTCC**TTAGGT**TTCC**ATGTT, CCCCG**GGAA**AG**TTCC**TGCCG
PRMT8	GGCAT**GGAA**AACCA**GGAA**GTTTC
PRPF19	TTCTG**GGAA**AGGGCAAT**TTCC**GTTAG
RAD1-BRIX1	TTCAC**TTCC**TCCGCGG**TTCC**TCGGA
RAD9B-VPS29	GTTTA**TTCC**CT**TTCC**CTAGA, TTGCG**GGAA**ACGAGTA**GGAA**CCGTCT**GGAA**ACGGA, CTCCC**TTCCTTCC**CTAGA, GGGAT**TTCC**CAA**TTCC**TCGCC
RAD17	CCAAC**GGAA**TTAACG**TTCC**GCGTC
RAD23A	AACCC**GGAA**GGC**GGAA**GCTGC
RAD23B	CGACA**TTCC**AGGACCGCC**TTCC**GCCCC
RAD51AP1-C12orf4	TGGGA**GGAA**AACTAAG**GGAA**AAGAC
RAD51B	AAAAT**TTCC**AAACAGGGTG**TTCC**CTTGT, GCGTT**TTCC**GCGG**GGAA**ACTGT
RAD51C(FANCO)-TEX14	TTTGG**GGAA**TCAAAAC**GGAA**TGGTG
RAD51D	ATCCG**TTCC**GTTT**GGAAC GGAA**GCTGG, AGCCT**GGAA**CCC**GGAA**GCGGC

Gene-Partner gene	Sequence
RAD52-ERC1	GGTGA**GGAA**CTG**GGAA**GCGGG, CCGTA**GGAA**GTGGACGCT**GGAA**GCCCG
RAD54L	AAATC**TTCC**C**TTCC**ATAGC, CACTA**TTCC**CGCCTC**TTCC**TTGGG
RAF1	ATGGG**GGAA**AAATGAACTC**GGAA**TTTAC
RASSF	CACTG**GGAA**AAGCAT**GGAA**AGACT, AGGAG**GGAAGGAA**GGGCAA
RB1-LINC00441	CAGGT**TTCC**CAGTTTAA**TTCC**TCATG, CGGGC**GGAA**GTGACGTT**TTCC**CGCGG
RBBP8	TTTGA**TTCC**ATG**TTCC**ACAGA
RBP14	CCCAG**GGAA**TGT**TTCC**AAAGA
RECQL-GOLT1B	ACGTC**TTCCGGAA**ACACG
RECQL5-SAP30BP	CCCGA**TTCC**CCC**TTCC**AGCTT, CCGAC**TTCC**GGGC**GGAA**AGGCA, AACAG**TTCCGGAA**CCAGC
REV3L-TRAF3IP2	GTTCG**GGAA**GGG**GGAA**CGCCA
REXO2	ACTCA**GGAA**ATAACTCCT**GGAA**GCAAA
RFC2	GGGGT**GGAATTCC**CATCT
RFC5	AGGGA**GGAA**GTC**GGAA**ACTGG
RHBDL2	GCCCA**GGAA**GCCT**GGAA**CGCAA
RIF1	GGCAG**GGAA**GGGATG**GGAA**GGGATG**GGAA**GGGAG
RMI2	CCCAT**TTCC**TCCGTTCA**TTCC**TAACT
RNF2	AGAGT**GGAA**GGTCATT**TTCC**CAGGA
RNF4	CGGCT**GGAA**ATCTA**GGAA**TG**GGAA**GGTTC
RNF44	GTAAG**GGAA**GGCCCTCACT**TTCC**CCATC, CTTAG**TTCC**CAGT**TTCC**CTGGC, ACCTG**TTCCC**CGCCTCTC**TTCC**TCCAC
RNF113A	GCTCC**GGAA**GAAGCGAC**GGAA**TCTGC
ROCK1	GCTTC**GGAA**CT**TTCC**CAGTG, GCTGG**TTCC**CC**TTCC**GAGCG
RPA2	TTTGA**GGAAGGAA**CTGAC
RPA3	TTTTC**TTCC**TCTTT**GGAA**TTAAA
RPS3	CCCCT**TTCC**TG**TTCC**TGCCT, GCCAC**TTCC**T**TTCC**TTTCA
RPM1	TTTTC**TTCC**AG**TTCC**AGAGT
RRM2B	CCAGC**GGAA**GCAGGGAGAT**TTCC**TTAGG
RTEL1	AAGCT**GGAA**CGCAGGAGA**GGAA**GGAGA
RUNX1	ATTCT**TTCC**CT**TTCC**CAGGC, TGGAG**GGAAGGAA**GGGCA, GCTGT**GGAA**AGG**GGAA**CAGTT
RUVBL1-EEFSEC	ACCCG**TTCC**GGCCC**GGAA**GC**TTCC**GCCCT

Gene-Partner gene	Sequence
SAMHD1	CCACT**TTCCTTCC**TCTG**GGAA**TGCAG, AATCA**TTCC**GGGTTC**TTCC**AGTTC, CTGTT**TTCC**TCTTCACTG**GGAA**GGTGC, GCTCT**TTCC**TCCCCCT**TTCC**ACCAG
SAT1	CCTCT**GGAA**AA**TTCC**ATTGT
SERPINE1	CTGGG**GGAA**AAC**TTCC**ACGTT
SETMAR	GTCAA**GGAA**G**GGAA**GCGCC**TTCC**AGGCC
SETX	GGCCT**TTCC**CGCAGTG**TTCC**CCTGG
SF3B3-COG4	CGTGT**GGAA**GCAAGAC**GGAA**GCATT
SFPQ	CTGTA**TTCC**TATGAGG**TTCC**ATAAT
SFR1	CGAGA**GGAA**ACTGGAT**TTCC**AGTTT, CTCTC**TTCC**CCTTTGTAAA**TTCC**TTGGG
SIRT1	CTTCA**GGAA**GACGT**GGAA**A**TTCC**CAGGG
SLC30A9	CATCC**TTCC**CATCT**TTCC**TCCCAT**TTCC**GAAAC, CCCCG**GGAAGGAA**GGCCT
SLX1A-BOLA2B	GCCAC**TTCC**GCT**GGAA**AACTCAC**TTCC**GCCCT, GCGGC**GGAA**CTCAG**GGAA**GGAGC
SLX4 (FANCP)	GCAGA**GGAA**GACC**GGAA**GCGAG
SMAD3	CGTGT**TTCC**CAGGAC**TTCC**TCCCC, GGACT**TTCCTTCC**CGGAG
SMARCB1	AGAGA**GGAA**TGGAGAAGGT**GGAA**GGTGT
SMC1A-RIBC1	GGTCC**TTCC**AA**TTCC**CGACC
SMC2	TCAAA**GGAA**TAAATAG**TTCC**GGCGC
SMC3	CAGCA**TTCC**ATGTG**TTCC**AAGGC, GGCGC**GGAA**CCT**TTCC**CCCTT
SMC4-IFT80	TCAAG**TTCC**A**GGAA**AGCGG, CTCCC**TTCC**TC**TTCC**CGCGA
SMC5-SMC5AS1	CGGTG**GGAA**C**GGAA**GTCGC
SMG1	CTCCC**TTCC**C**TTCC**ATCGT, GTGCT**TTCC**G**GGAA**GCGTT
SMO	ACGAT**TTCC**ACTCATCTCT**TTCC**CCCGG
SMUG1	AGCAT**TTCC**GGC**GGAA**GTGGC, GTGGG**GGAA**A**GGAA**CC**GGAA**ACGGG
SOX4	TCGGG**TTCC**AAGCCAATG**GGAA**GCCCG
SP1	CTGGT**TTCCTTCC**AAGCC
SPATA22	GATTC**TTCC**A**GGAA**CAACA, GTCGA**GGAATTCC**C**GGAA**ACCTC
SPIDR	CCCGG**GGAAGGAA**GCTCG
SPTAN1	CCTCG**GGAA**AGTGAGCA**GGAA**GAGAC
SSRP1	ACGCG**GGAA**AAGC**TTCC**CCGGT
STAT3	GGACA**TTCC**GGTCATC**TTCC**CTCCCT
STRA13	CCGGC**TTCCGGAA**GGTGA

Gene-Partner gene	Sequence
STUB1	AACTC**TTCC**CGATACCTGA**GGAA**GGGCG
SUMO1	CCCAT**TTCC**CGCCTTGTCT**TTCC**TCTCT
SUPT16H	TTGTG**GGAAGGAA**CTAAA, GCTCT**TTCC**GCTCCCCC**TTCC**TTTGC
SUZ12	TTTTT**TTCC**TCCCTCC**TTCC**CTCCT
SWI5	TCAGT**TTCC**CAAGACCTG**TTCC**ACAGA, TCCCC**TTCC**AGCT**GGAA**ATTTA, CTACA**TTCC**ACTCCTAGGG**GGAA**CATCA
SYNE2	CAAGG**GGAA**GGA**GGAA**CCCAG, CCTAC**TTCC**AAGACCCA**GGAA**TCTAC
TCEA1	ACGGG**TTCC**ATTT**TTCC**CCGTA, CAAAG**TTCC**ATGCTC**GGAA**TCTGC
TDP1-EFCAB11	GGCAA**GGAA**CGTGGGGCGAG**TTCC**TTTTC (11 nucleotide distance)
TDP2-ACOT13	ACTTC**GGAA**GAGCT**GGAA**AGTCC
TDRD3	TTTTG**GGAA**GACCAAAC**GGAA**TACCC, TCCCC**TTCCTTCC**GTAAC, TACCC**TTCC**GCCTG**TTCC**TCTCT
TERT	TCCCC**TTCC**T**TTCC**GCGGC
TICRR	AAGTT**TTCC**TCGGTCTTG**GGAA**ACGTG, GCTGT**TTCC**CTGAA**GGAA**GGGAC
TIRAP	CCTTT**GGAA**AAG**TTCC**ATCTC
TK1	TAAGC**TTCC**TTCTT**GGAATTCC**AATCT, TCTTC**TTCC**AA**GGAA**CCTTGCTTG**GGAA**ACCCA
TONSL	CGTAC**TTCC**C**GGAA**TGCCC
TOP2A	TCAGT**TTCC**TCA**GGAA**AACGA, ACCCC**TTCC**CGC**TTCC**AAAGC, ATCTC**TTCC**AAGCT**TTCC**GCACG
TOPBP2	ATTGA**GGAA**ATCCTTTCT**TTCC**CTGGC, GTCAC**TTCC**ACC**GGAA**AAGGC
TP53-WRAP53	TCCAT**TTCC**TTTGC**TTCC**TCCGG
TP63	ATCAA**GGAA**T**TTCC**CTGTC
TREX1	GCTTC**TTCC**AGAGG**TTCC**CCAAC, GCCGC**GGAA**AC CGATGT**GGAA**GACCC
TREX2	CTCCC**TTCCTTCC**CCAGC
TRIM56	CTCCA**GGAA**GCCTGTGCTG**TTCCC**TCAG
TRIP12-FBXO36	GAGGG**GGAA**TTAG**TTCC**TGCTA
TTC5	TTTGT**TTCC**AGGATCTG**GGAA**AGAAA
TYMS	CCGCA**GGAA**AACGTG**GGAA**CTGTG, CCAGG**TTCC**CGGGT**TTCC**TAAGA, CCGCG**GGAA**AAGGCGCGC**GGAA**GGGGT
UBA1	CCCAA**GGAA**GAAT**TTCC**AGCAC, ACACG**TTCC**GT**TTCC**TC**TTCC**CACCC
UBA2	CGCCC**TTCC**CCCACCCGC**TTCC**GGCCG

Gene-Partner gene	Sequence
UBB	TGCAA**GGAA**GT**TTCC**AGAGC, ATATT**TTCC**TAAAGAA**GGAA**GAGAA
UBC-MIR5188	GTACA**GGAA**GGT**GGAA**GAACA, GGGGT**TTCC**GCCTCTTTT**TTCC**AAATT
UBE2B-CDKL3	CTTCA**GGAA**GCCCAGGG**GGAA**CCGCG
UBE2T	CTAAC**TTCC**ACTTGAACAT**TTCC**AGTGATGAA**GGAA**TTCAC, ACGAT**TTCC**AGCTCC**TTCC**TTGGT
UBE2V1	GCGCC**GGAAGGAA**TCCTG
UBE2V2	ACAAG**GGAA**TTGC**GGAA**ACAGC
UBE2W	TGGTT**GGAA**ACGAAATA**GGAA**AAAAA
UBR5	ATAAT**TTCC**TTACTT**TTCC**AATAA
UHRF1	AGGCG**GGAA**AACGAGGCG**GGAA**AAGAC
UNG	GGGCA**GGAA**CTTTTC**TTCC**CAGCC
UPF1	GATGG**GGAA**ACTGAG**TTCC**AAGCA
USF1	GAATG**GGAA**TCAAGA**TTCC**TGTCA, CTTCT**TTCC**T**GGAA**TGAAA
USP1	GCGCG**GGAA**CCCTG**GGAA**GCTCC
USP3	CACCC**TTCC**CGGGGCCGG**GGAA**GCGGC, GACTA**GGAA**AGTCACTTC**GGAA**CACAG, GGCCT**GGAA**AGGC**GGAA**GCCTC
USP28	TGATG**GGAA**ATCCTTTA**TTCC**ACGGT, GCAGT**TTCC**CACGGCGGG**GGAA**CAGTT
USP47-LOC102724878	GAGAA**GGAA**G**TTCC**CT**GGAA**GAGGG
UVSSA	AGACC**GGAA**C**TTCC**TTTCG
VCP	GAGAA**TTCC**AATCCGTCGA**GGAA**GCGTA
VWA2	AAAAA**GGAA**AT**GGAA**AACCT
WRN	AGGTG**GGAA**GATG**GGAA**TGAGG
WRNIP1-MYLK4	GGGCC**GGAA**GACGACCCC**TTCC**TTTCG
XIAP	CATCC**TTCC**CTTCTT**GGAA**ACAGA, CTTTC**TTCC**ACTA**TTCC**TCAAC
XPC-LSM3	CATTT**TTCC**TGAGTCT**GGAA**AAAGC, GCTCT**TTCC**TGC**TTCC**CGCAG
XRCC1	GCTAA**GGAA**CGCAGCGCTC**TTCC**CGCTC
XRCC3-ZFYVE21	CGGCG**GGAA**GAGGAGTGC**GGAA**CCCGC
XRCC4-TMEM167A	GTTTT**GGAA**GATACC**GGAA**GTAGA
YBX1	CTCGT**GGAA**GTCACG**TTCC**TTCTG
ZC3HAV1(PARP13)	GCTCT**TTCC**G**GGAA**TGGGT
ZNF143-LOC644656	CCAAT**GGAA**AACC**GGAA**GCGTC, ACGAA**GGAA**TTGTT**GGAA**AATTT

Gene-Partner gene	Sequence
ZNF668-ZNF646	GGGAG**GGAA**G**GGAA**AGAG**GGAA**AGGAG, AGGGG**GGAA**GA**GGAA**GGAGG, TACTA**GGAA**ACA**GGAA**GTGTC, AAAGC**TTCC**CCGCGAAAC**TTCC**GCTTC, TTAAA**GGAA**ATGTTGT**GGAA**TATAA
ZNRD1-ZNRD1AS1	TGGTG**GGAA**AATTTGCT**GGAA**GCGCAG, CCCCT**GGAA**AGGG**TTCC**AAGTC, GTCTG**GGAATTCC**GGGCG

Table 1. GGAA motifs located in the 5′-upstream regions of human genes encoding DNA-repair associated factors. Duplicated GGAA (TTCC) motifs (bold) that are located between 540-bp upstream and 90-bp downstream of the putative transcription start sites (TSSs) of DNA repair-associated protein encoding genes are shown. Several of them have bidirectional partner genes. In that case, extra sequences containing both of the most upstream were surveyed. Nucleotide sequences contained in the 5′-upstream of the partner cDNAs are also included.

3.1. Classification of DNA repair genes whose upstream regions contain duplicated GGAA motifs

Numbers of genes (Table 1) encode proteins with multiple functions. However, they could be categorized into several groups as follows:

1. Nucleotide excision repair (NER); *ATR, CDKN1A, ERCC1, ERCC2(XPD), ERCC3(XPB), ERCC4 (XPF), GTF2H1, GTF2H2, GTF2H3, H2AFX, LIG1, PARP1, POLD1, POLD3, POLD4, RAD23A, RAD23B, RFC2, RFC5, RPA2, RPA3, UVSSA, XPC, XRCC1*... NER is a DNA repair system that is executed with several functional proteins, which recognize a lesion to form TFIIH complex to excise the lesion introduced DNA chain and the gap is filled by DNA polymerases [71].

2. Transcription coupled repair (TCR); *APEX1, BRCA1, CDK1, CDK2, CDKN1A, CDKN2A, ERCC1, ERCC2, ERCC3, ERCC4, GSTP1, GTF2H1, GTF2H2, GTF2H3, LIG1, MRE11A, NBN, PARP1, POLD1, POLD3, POLD4, POLH, POLR2A, POLR2B, POLR2F, POLR2G, POLR2I, PRKDC, RFC2, RFC5, RPA2, RPA3, SP1, STAT3, TERT, TP53*...TCR is thought to regulate genomic integrity. This process begins with unwinding the double stranded DNA by TFIIH, the next step is that the damaged strand is incised apart by XPF, XPG and endonucleases, then gap is filled and finally the nick is ligated [72].

3. Fanconi anemia proteins*; ATM, ATR, BRCA2 (FANCD1), BRIP (FANCJ), CHEK1, ERCC4(FANCQ), FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, NBN, PALB2 (FANCN), LMNA, RAD51C (FANCO), SLX4(FANCP)*...Encoded proteins are involved in Fanconi anemia pathway that plays a part in the repair of inter strand cross links [73]. Notably, all genes that encode protein components in the Fanconi anemia core complex are listed in Table 1.

4. Double strand break (DSB) repair, Non homologous end joining (NHEJ); *APC, APEX1, ATM, ATR, BLM, BRCA1, BRCA2, CHEK1, DCLRE1A, DCLRE1B, DCLRE1C, DDX1, ERCC1, ERCC4, FEN1, LIG1, LMNA, MCM8, MRE11A, NBN, PARP1, RBBP8, POLA1, POLB, POLH, POLL, POLM, POLR2A, RAD51AP1, RAD51B, RAD51C, RAD51D, RAD52, RECQL, RECQL5, SP1, TERT, TP53, TREX2, XRCC4*... DSBs are caused by stresses on

chromosomal DNAs, such as irradiation of ultra violet or X-ray, and alkylating agents. Unrepaired DSBs will lead to collapse of stalled replication forks and in response to uncapped telomeres [74]. Some of the genes that encode protein components in the MRE11 complex are listed in Table 1. Not only serving as regulator of the mammalian DNA damage response, the MRE11 complex plays an important role in the maintenance of telomeres [75].

5. Base excision repair (BER); *APC, APEX1, BRCA1, BRCA2, CDKN1A, CHEK1, ERCC1, ERCC2, FEN1, LIG1, NBN, NEIL1, NEIL2, PARP1, PARP2, POLA1, POLB, POLD1, POLD3, POLD4, POLG, POLH, POLI, POLL, POLL, POLQ, RAD23B, RECQL5, RPA2, RPA3, RPS3, TP53, TREX1, UNG, WRN, XPC, XRCC*... BER is a fundamental repair system to eliminate nucleotide-bases from mutated nucleotides that is recognized by AP endonucleases. FEN1 and Ligases fill the gap to ligate DNA ends [76, 77].

6. Apoptosis; *ABL1, APC, BARD1, BCL2, BCR, BLM, BRCA1, CNKN1A, CDKN2A, CHEK1, ERCC1, ERCC2, ERCC3, ERCC4, HMGB2, KRAS, LMNA, MRE11A, PARG, PARP1, PARP4, RAD23A, RAD23B, RAD51B, SIRT1, SUMO1, TERT, TOP2A, TP53, TP63, XIAP*... Apoptosis or programmed cell death is executed by a number of proteins, including mitochondrial protein BCL2 and tumor suppressor p53 [48, 51]. It is thought to be an important process to eliminate cells with unrepairable DNA damage.

7. Mitochondrial functions; *ADPRHL2 (ARH3), APEX1, ATM, BARD1, BCL2, BRCA1, BTG2, CDKN1A, CDKN2A, ERBB2, FEN1, FOXO3, LMNA, PARG, POLG, SIRT1, STAT3, SUMO1, TERT, TP53, TP63, XIAP*... Mitochondria and nuclei are communicating to regulate each other [6-9]. Several of the DNA repair factors, including p53 and BRCA1, have been shown to localize in mitochondria [78, 79]. It has been shown that mitochondrial matrix-associated proteins are poly(ADP-ribosyl)ated [80]. Poly(ADP-ribosyl)ation, which is catalyzed by PARP enzymes, is a modification of proteins utilizing NAD^+ molecule as a substrate [81]. The NAD^+/NADH ratio is thought to regulate mitochondrial metabolism. A recent study showed that decrease in NAD^+/NADH ratio, which is thought to occur by an aberrances in mitochondria, does not only enhance cancer progression but also metastasis [82].

8. Response to IFN; *ABL1, BCL2, BCR, FOXO3, IL18, PARP1, PRKDC, RUNX1, RUVBL1, SAMHD1, SP1, STAT3, TERT, TP53, TREX1*... Duplicated GGAA (TTCC) motifs are found in number of the 5′-upstream regions of the human Interferon Stimulated genes (ISGs) [61]. The observation suggests that expression of some of the DNA repair factor-encoding genes might be up-regulated by IFN-induced signals.

3.2. The GGAA (TTCC) motifs are often present in the 5′-flanking regions of the genes that encode protein modification factors

PARP enzymes and p53, which have multiple functions in DNA repair process, are thought to affect mitochondrial metabolism [29, 83]. We previously reported that 5′-upstream regions of many of the mitochondrial function associated genes contain duplicated GGAA (TTCC) motifs [12]. Therefore, mitochondrial function could be up-regulated when cells encounter

with various stresses, including DNA damage, viral infections, or tumorigenesis. It is noteworthy that PARP enzymes consume NAD^+ to synthesize poly(ADP-ribose)s on various target proteins, including p53 [18, 19]. Given that NAD^+ is an essential molecule for energy metabolism, the ratio of inner cellular NAD^+/NADH may keep balance of mitochondria/DNA repair system. SIRT1, which is known as a NAD^+ dependent de-acetylating enzyme, is not only involved in controlling life spans of organisms but also DNA repair system with PARPs [84]. Besides affecting transcription by its de-acetylating activity, SIRT1 may indirectly contribute to regulate inner cellular acetyl-CoA level [85]. SIRT3, which localizes in mitochondria, catalyzes de-acetylation of acyl-CoA dehydrogenase and acetyl CoA synthase 2 [86-88]. It should be noted that *SIRT3* gene is head-head configured with *PSMD13* gene [89], and that the bidirectional promoter contains a sequence, 5′-ACTAG**GGAA**C**TTCC**TCTAC-3′ [12]. It is important to remind that both the NAD^+ and the acetyl-CoA are essential molecules in energy metabolism. Thus, GGAA-mediated transcription might be a biologically constitutional response to nutrition stress.

Not only the ubiquitin encoding genes, *UBB* and *UBC*, ubiquitin metabolism factor encoding genes, including *UBE2B*, *UBE2T*, *UBE2V1*, *UBE2V2*, *UBE2W*, *UBR5*, *UHRF1*, *USP1*, *USP3*, *USP28*, and *USP47*, are included in Table 1. Protein ubiquitination has been suggested to regulate DNA repair [90]. Notably, SUMOylation, which is a modification of proteins with Small Ubiquitin-like Modifier [91], plays an important role in DNA repair [92, 93]. The duplicated GGAA motif is also present in the *SUMO1* promoter [50]. Furthermore, UBA1, whose encoding gene is listed in Table 1, is a SUMO1 activating enzyme [94].

3.3. Possible roles of the duplicated GGAA motif in the 5′-upstream regions of DNA-repair genes

Genome wide analysis of the human promoters revealed that c-ETS binding element is frequently found with another c-ETS binding element [95, 96]. Redundant occupation of the duplicated GGAA motifs by Ets family proteins seems to be a complicated system, but this would enable finely tuned regulation of each promoter through altering composition of Ets family or GGAA-binding proteins, including GABP and STATs, in the nucleus in response to cellular signals [95].

4. Bidirectional promoters that regulate DNA repair factor-encoding genes

From the surveillance of the human DNA data base, not only mitochondrial function associated genes but also DNA repair factor encoding genes have head-head oriented partner genes [12]. Recent studies on RNA sequencing revealed a wide variety of transcripts, and the human DNA data base is continuously updated. Therefore, numbers of known bidirectional promoters are increasing day by day. As the reason why so many genes have bidirectional partners has not yet been elucidated, there is great value in investigating the role of bidirectional promoters driving transcription of DNA-repair factor encoding genes.

4.1. Surveillance of the bidirectional promoters from human genomic database

We have reported that a lot of human mitochondrial function associated genes have a bidirectional partner [12]. Moreover, several DNA repair associated genes are head-head configured with another gene [11]. Re-surveillance of DNA repair factor-encoding genes revealed that a number of the genes have opposite direction transcribed partner genes, utilizing the same regulatory region as their common promoter (Table 1). Although the number of the bidirectional gene pair is increasing according to recent findings of transcripts with next generation sequencing, at least 95 gene pairs were identified from the surveillance of the 358 DNA repair associated genes whose promoter contains GGAA (TTCC) motifs. The observation suggests that duplicated GGAA (TTCC) motifs and the binding factors may play a part in the bidirectional transcription of both mitochondrial function- and DNA repair-associated genes. However, these genes are not always simply controlled by GGAA-motif alone. For example, Sp1 binding element or GC-box is co-localized with ETS binding motifs in human promoters with 28.4% occurrence [95]. Co-operation of the GABP binding motif with Sp1/3 and YY1 binding sites is required for murine *Gabpa-Atp5j* bidirectional promoter [97]. These observations suggest that another *cis*-element, such as GC-box, may play a role in the co-operative transcription.

4.2. Biological relevance of bidirectional transcription

It has been reported that many cancer or DNA repair associated genes have bidirectional partner genes, and that tandem repeated ETS binding sites are frequently found in the 5'-upstream regions of both genes [98-101]. Therefore, expression of many DNA repair factor encoding genes is thought to be regulated by TFs that bind to GGAA motifs.

Surveillance of the human genomic sequence database revealed that several ISGs have bidirectional partner genes [61]. Similar to the bidirectional promoters involved with DNA repair factor encoding genes, bidirectional ISG promoters contain duplicated GGAA motifs. They are *BAG1-CHMP5*, *BLZF1-NME7*, *EIF3L-ANKRP54*, *CCDC75-HEART5B*, *IFI27L1-DDX24*, *PARP10-PLEC*, *PSMA2-MRPL32*, *RPL22-RNF207*, and *TRADD-FBXL8* [61]. It is noteworthy that the bidirectional gene pair *HSPD1-HSPE1*, which encodes the mitochondrial chaperon proteins HSP60 and HSP10, respectively, has been reported to be regulated by IFN gamma [102]. These findings suggest that promoters of the DNA-repair and mitochondrial function associated genes that carry duplicated GGAA-motifs could be simultaneously regulated by IFN-induced signals.

5. Cellular senescence and cancer generation might be simultaneously regulated at transcriptional level

Introduction of several transcription factors (OSKM or Yamanaka factors) into somatic cells could reprogram and generate induced pluripotent stem (iPS) cells [103]. Recently, it was demonstrated that three transcription factors, *Blimp1*, *Prdm14*, and *Tfap2c*, direct epiblast-like

cells into primordial germ cells [104]. Moreover, transcription factor C/EBPα enhances effects of the OSKM factors to reprogram B cells [105]. These lines of evidences imply that the transcriptional profile determines cell fate towards proliferation, cell cycle arrest, differentiation, senescence or programmed cell death. Furthermore, it has been postulated that nutrient or metabolite state may contribute to affecting the balance between quiescence and proliferation of stem cells [106]. In this article, we would propose a hypothesis that DNA-repair and mitochondrial functions are regulated by the same or similar mechanisms that affect transcription of various genes *via* common duplicated GGAA motifs. The scenario is that transcriptional dysregulation should proceed to characteristics of cancer, including mitochondrial dysfunction and genomic instabilities. Conversely, cancer and malignant tumors could be reprogrammed to benign state if transcriptional state in the cells were altered.

5.1. Effect of caloric restriction (CR) mimetic drugs on telomere associated protein-encoding gene promoters

Loss of function mutations on the *WRN* gene, which encodes telomere regulating RecQ helicase, can lead to cancer or premature aging syndrome [107, 108]. On the other hand, caloric restriction (CR) can extend life spans of various organisms [109], and thus CR mimetic drugs may have an anti-aging effect. We therefore hypothesized that CR mimetic drugs activates transcription of telomere-associated genes and demonstrated that promoter activities of the human shelterin encoding genes are up-regulated by 2-deoxy-D-glucose (2DG) and Resveratrol (Rsv) in HeLa S3 cells [110].

2DG and Rsv, which are known as a potent inhibitors of glucose metabolism [109], and an activator of sirtuin-mediated de-acetylation [111], respectively, are often referred as CR mimetic drugs. We observed moderate activation of telomerase activity in HeLa S3 cells with 2DG and Rsv treatment [110, 112], suggesting that CR mimetic drugs have protective effects on telomeres by inducing telomerase activity along with up-regulating expression of the telomere maintenance factor-encoding genes. The human *TERT* (h*TERT*) promoter has been well characterized with c-Ets, GC-box, E-box and other TF-binding elements that are located in its 5′-flanking region [113, 114]. GC-boxes and Sp1-binding sites are frequently found in the human *TERT*, *WRN* and shelterin protein-encoding gene promoters with duplicated GGAA elements that present adjacent to TSSs [110, 115].

Interestingly, both duplicated GGAA-motif and GC-boxes are contained within 500-bp upstream of the TSS of the human *SIRT1* gene [116]. SIRT1, which plays a role in NAD^+ dependent de-acetylation of various proteins including histones, PGC-1α, FOXO1, p53 and HIF1α, is proposed to regulate aging and the healthspan of organisms [117]. Human *SIRT1* gene expression is regulated by PPARβ/γ through Sp1 binding elements [118]. Therefore, signals evoked by CR or CR mimetic drugs might induce Sp1 or GC-box binding TFs, thus simultaneously up-regulating expression of *TERT*, *WRN*, *SIRT1*, and the shelterin-encoding genes. Given that the CR imposes a stress on cells due to the lack of nutrients or energy to survive, cells need to stop growth but need to keep the integrity of chromosomes and telomeres without replication of their genome. Under these circumstances, cells may require full commitment of mitochondria to drive TCA cycle and OXPHOS generating more ATP mole-

cules than glycolysis does. Therefore, CR mimetic compounds with ability to induce telomere maintenance factor encoding genes might be anti-aging drugs simultaneously up-regulating expression of mitochondrial function associated genes.

5.2. Mechanisms that regulate aging or lifespan via mitochondria and metabolic state

Genetic studies of *C. elegans* implied that the insulin/IGF-1 signaling pathway regulates the lifespan of animals [119]. Insulin/IGF-1 signaling and glucose metabolism are thought to be associated with several diabetes/obesity controlling factors, including AKT, FOXO, mTOR and AMPK [120]. The mTOR is a component of mTORC1 and mTORC2 that play key roles in signal transduction in response to changes in energy balance [120]. Recently, it was reported that mTORC1 in the Paneth cell niche plays a role in calorie intake by modulating cADPR release from cells [121]. AMPK is known to be a sensor for energy stress and DNA damage to induce phosphorylation of various TFs, such as FOXO, PGC-1α, CREB and HDAC5 [120, 122]. Moreover, AMPK regulates SIRT1 activity by modulating NAD^+ metabolism [122].

Mitochondrial functions are known to affect lifespan of organisms [123]. Furthermore, a cross talk between telomeres and mitochondria is suggested to regulate aging [124]. This concept was implied from a *Tert* knock down experiment that indicates telomere dysfunction causes suppression of PGC-1α in a p53-mediated manner [6]. The tumor suppressor p53 has been suggested to affect aging of organisms as a pro-aging factor [125]. It does not only affect cell cycle arrest and apoptosis, but also play a role in mitochondrial respiration and glycolysis [126, 127]. These lines of evidences strongly suggest that p53-mediated signaling is transferred to both telomeres and mitochondria to control cellular senescence. Although no canonical GC-boxes are found, duplicated GGAA-motifs are located near the TSS of the human *TP53* promoter (Table 1). Detailed analysis of the *TP53-WRAP53* bidirectional promoter region revealed that both the duplicated GGAA motif and a putative E2F binding sequence are involved in the response to Rsv [128]. Therefore, various stresses from DNA damage, viral infection, or lack of nutrients, will activate expression of genes encoding DNA repair/mitochondrial/telomere maintenance-associated factors *via* duplicated GGAA-motif with help from other *cis*-elements, including GC-box and E2F elements.

5.3. Implication of transcriptional control on genes that encode TCA cycle enzymes

It has long been argued how and why cancers are generated. Recently, diagnosis of cancer and diseases that are thought to occur from genomic alterations could be analyzed by second-generation sequencing [129]. In general, it has been thought that cancer is a genetic disease with several mutations on driver genes, including *PIK3CA*, *IDH1* and *RB1* [130]. Another aspect of cancer is that it is a metabolic disease [79]. It is widely known that cancer consumes more glucose to produce ATP by glycolysis or fermentation. The metabolic state of the cells could be referred to as the "Warburg effect" [131]. Importantly, TCA-cycle enzymes, FH (Fumarate hydratase) and SDH (succinate dehydrogenage) have been suggested as tumor suppressors [132]. We have confirmed that duplicated GGAA motifs are present near TSSs of the *CS*, *ACO2*, *IDH1*, *IDH3A*, *IDH3B*, *SUCLG1*, *SDHAF2*, *SDHB*, *SDHD*, *FH*, and *ACLY* genes that encode enzymes in the TCA-cycle [12]. In this chapter, it was shown that a number of the

http://dx.doi.org/10.5772/59588

5′-upstream regions of DNA repair factor- and IFN responding factor-encoding genes contain duplicated GGAA (TTCC) motifs near their TSSs. The observation suggests that expression of genes encoding TCA cycle enzymes is mediated by GGAA-motifs in a similar manner to that of DNA repair factor encoding genes.

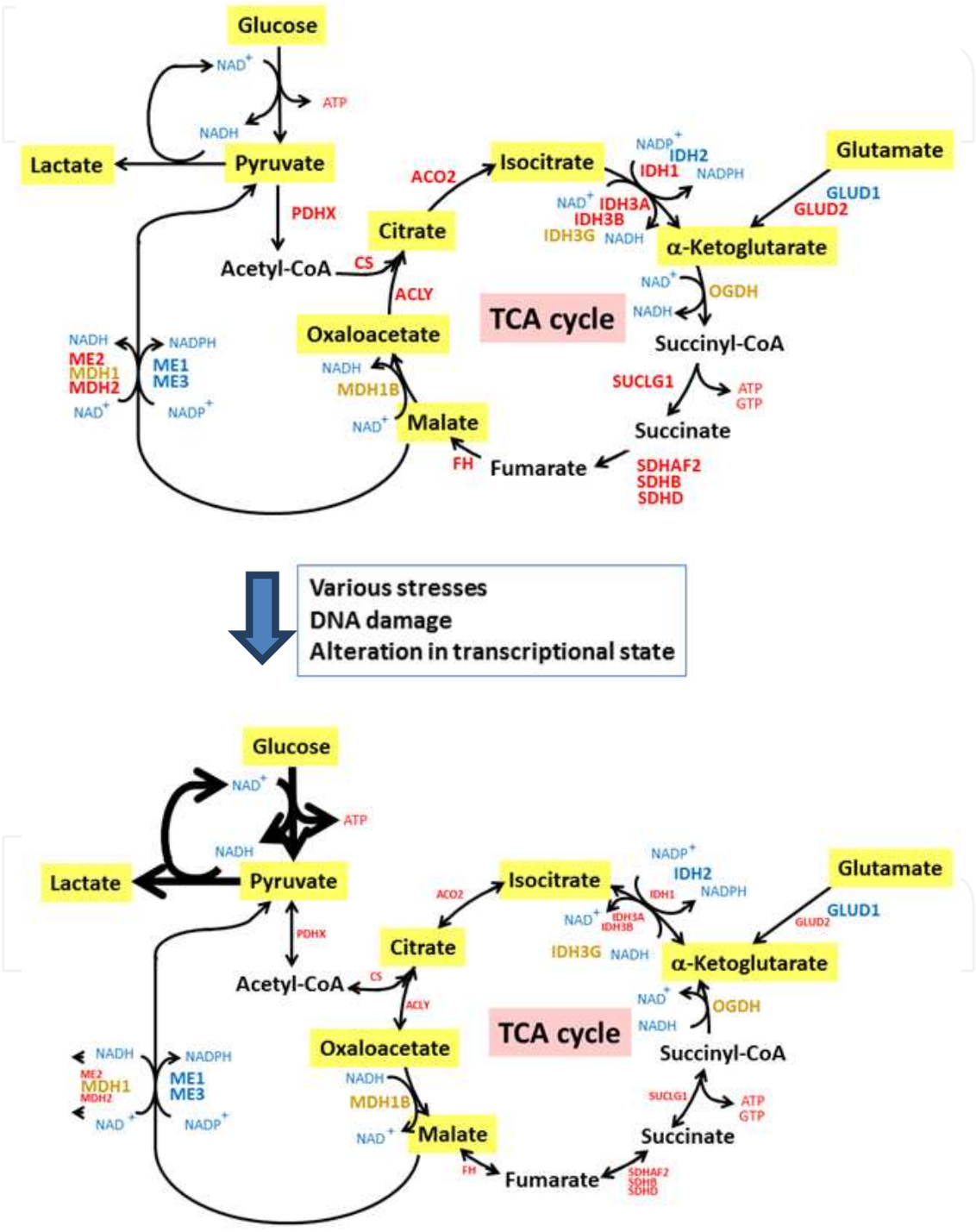

Figure 1. Dysfunction of tricarboxylic acid (TCA) cycle, which could be caused by alteration of GGAA-dependent transcription, may enforce the "Warburg effect". Duplicated GGAA-motifs are contained in the 5′-upstream regions of the

ACO2, *GLUD2*, *IDH1*, *IDH3A*, *IDH3B*, *MDH2*, *ME2*, *SUCLG1*, *SDHAF2*/*SDHB*/*SDHD*, *FH*, *ACLY*, *CS*, and *PDHX* genes (red). The activity of the IDH3 complex, OGDH, and MDH1B will be reduced when NAD^+/NADH ratio was attenuated according to the poly(ADP-ribosyl)ation when cells encountered DNA-damage. Compounds highlighted in yellow indicate metabolites that are produced when dysfunction of mitochondria and PARP activation has occurred, which push the cycle in the counter clockwise direction (reductive carboxylation). When FH and SDHs do not work sufficiently, glutamate will be used as a source to process TCA-cycle. Various cellular stresses, including chemicals, X-ray and UV irradiation, virus infection, and aging, may alter the quality and/or quantity profile of the GGAA-binding factors in a normal cell (upper panel). That will lead to disruption of the mitochondrial- and DNA repair function-associated gene expression. Repeated DNA-damage will enforce PARP activity to consume and deplete NAD^+ molecule from cytoplasm and mitochondria. When NAD^+/NADH ratio decreased to cause dysfunction of the TCA-cycle, cells would synthesize ATP by glycolysis or fermentation (lower panel). The consequence could be referred to as the "Warburg effect".

5.4. Regulation of rate limitting factors in the DNA repair system

As noted in **3.2.**, PARP, which localizes in mitochondria, may play a key role as one of the rate limitting factors in the DNA repair system. Poly(ADP-ribosyl)ation is essential for DNA repair, especially in cells that have deficiencies in BRCA, which is also known to localize in mitochondria [78, 79]. Therefore, highly potent inhibitors for PARP1 have been tested in different clinical trials [47]. Inhibition of the PARP enzyme will not only prevent over consumption of the NAD^+ molecule, but it also blocks DNA repair systems in cancer cells. This balance in metabolism/DNA repair should be taken into account for treatment of cancer patients. The other key factor in mitochondria is the p53, which is frequently referred as a "gurdian of the genome" [27, 28]. Although it has not been elucidated which TFs play essential roles in the regulation of those rate limitting factors in DNA repair, cells have some systems to monitor metabolites. For instance, C terminal-binding protein (CtBP), which is a transcriptional repressor of tumor suppressors [133], regulates *BRCA1* gene expression in a NAD^+/NADH ratio-dependent manner [134]. This implies that a metabolic swich mediated by CtBP plays a role in the regulation of the genes encoding DNA repair factors.

5.5. Alteration in transcriptional profile may cause cancerous state

It has been postulated that epigenetic and/or transcriptional changes play a role to determine chromatin states in tumor cells [135]. Recent genomic studies indicated alterations of gene expression in many human diseases [136, 137]. The transcriptome indicating *cis*- quantitative trait loci (QTLs) has been reported as value to reveal gene expression and transcription state in cells from patients of specific disease [138]. Cancer incidence in humans increase exponentially with age, suggesting that aging is the strongest demographic risk factor for most human malignancies [139, 140]. This has been mainly explained by reactive oxygen species (ROS) generation and accumulation of DNA damage on chromosomes or increased genomic stability, including telomere shortening [140]. Moreover, hypoxia, which will attenuate DNA damage response causing an increased mutation rate and chromosomal instability, has been suggested to modulate senescence [141, 142]. Importantly, aging is accompanied with epigenetic change and alteration of gene expression profile [143, 144]. Numerous GGAA motif-binding TFs acting as positive and negative transcriptional regulators, could drive mitochondrial- and DNA repair factor-encoding genes. The redundancy of the binding factors to the related sequences may help to control expression of a specific gene with accuracy, and subtle changes in the

profile of the TFs would not cause severe abnormalities in normal cells. However, repeated cell division and extracellular signals will gradually disturb the balance of TFs that bind to GGAA (TTCC) motifs, and finally lead to dysregulation of mitochondrial functions, DNA-repair system, and IFN-response simultaneously. At this stage, abnormalities in metabolism, mutations on DNAs, and aberrant IFN response would be observed in the cells. These features could be referred to as characteristics of cancer and malignant tumors. Moreover, DNA damage-inducing signals will activate poly(ADP-ribosyl)ation to lead to over consumption of NAD^+ molecule for poly (ADP-ribose) synthesis. The reduction of NAD^+/NADH ratio in mitochondria may in turn reverse the direction of the TCA cycle. If the TCA cycle cannot meet demand for ATP levels, cells will abandon dependence on the normal respiratory system in favour of up-regulating glycolysis or fermentation (Fig. 1).

6. Concluding remarks

It remains unclear how the GGAA motif has been duplicated and incorporated into specific regulatory regions of various genes. However, the duplication of TF binding site might have been advantageous for organisms in the course of evolution. The crystal structure of mouse Elf3 with type II TGF-β receptor promoter was reported [145], representing an association model of the *ets* motif binding protein with the duplicated GGAA motifs. Very recently, it was shown that binding sites for MYC and its partner MIZ correlate with Pol II binding and transcription start site [146], implying that two adjacent TF-binding sites play significant roles in the regulation of transcription of multiple genes. At least twenty seven ETS family proteins and other TFs, including GABP, NF-κB/c-Rel, and STAT proteins, recognize the sequence. Therefore, the transcriptional efficiency could be determined only by the distance between GGAA (TTCC) sequences, variation of the flanking sequences and the combination of binding factors, which might have acquired variations as a consequence of evolution.

It has been shown that a lot of head-head configured gene pairs are contained in human genomes [99]. In this chapter, we proposed a mechanism that alterations in the transcriptional state in the cells lead to insufficient mitochondrial function accompanied with impaired DNA repair system. In this regard, cancer could be referred to as a "transcriptional disease". Given that introduction of the four OSKM (Yamanaka) factors enables reprogramming of cell, enforced expression of some TFs could reprogramm metabolic state in cancerous cells [103]. In order to assess the possibility, elucidation of how human genes, especially those that encode mitochondrial function- and DNA repair-associated factors, are regulated by GGAA motif-dependent transcription system, should be done [128]. If the mechanism were revealed, scientists could establish gene therapy to let pre-cancerous cells regain normal TCA cycle/respiration from unhealthy ATP-synthesis, or get rid of "Warburg effect". In addition, this therapy will up-regulate DNA repair system. We believe that the concept is valuable, though not yet fully cultivated, to find a way to next generation cancer treatment with much lower side effects.

Acknowledgements

The authors are grateful to Kaori Inoue and Sayaka Ishibashi for discussion and outstanding technical assistance. This work was supported in part by JSPS KAKENHI Grant Number 24510270 and a Research Fellowship from the Research Center for RNA Science, RIST, Tokyo University of Science.

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