Chapter 5

A New Insight into the Development of Novel Anti-Cancer Drugs that Improve the Expression of Mitochondrial Function-Associated Genes

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Abstract

Recent analyses of the whole genome sequencing data enable us to predict cancer incidence for healthy people at present. In addition, metabolome analyses rediscovered that "cancer is a metabolic disease". Importantly, it has been suggested that mitochondrial dysfunction might precede the metabolic change. In this chapter, we would discuss if "cancer is a transcriptional disease". Analyzing 5′-upstream non-protein-encoding regions of the human mitochondrial function-associated genes, we speculate that mitochondrial functions could be recovered or improved at a transcriptional level. In the near future, novel chemo-/gene-therapies might be applied to treat cancer patient converting cancerous cells into normal differentiated cells.

Keywords: cancer, CTCF (CCCTC-binding factor), DNA repair, ETS (E26 transformation specific), gene expression, GGAA, HMGB (High mobility group box), ISG (Interferon stimulated gene), metabolism, mitochondria, NAD^+, PARP inhibitors, poly (ADP-ribosyl) ation, PARP (poly(ADP-ribose) polymerase), transcription, transcription factors, Warburg effect

1. Introduction

We have already learned that "cancer is a genetic disease". Recent high-impact research has shown the genomic/genetic differences between cancer and normal cells using methods such as next-generation sequencing [1, 2]. The analysis of the whole genome sequencing data will even enable us to predict the incidence of cancer in healthy individuals [3]. More

importantly, recent metabolome analyses have led to the rediscovery that metabolites could be biomarkers for cancer and its development [4]. The "Warburg effect", which was shown by Dr Otto Warburg over 60 years ago, is the most essential discovery in the field of cancer science [5]. The "Warburg effect" refers to abnormal metabolism in cancer, which mainly utilizes glucose to produce ATP by glycolysis. In this regard, "cancer is a metabolic disease". This is not only important as an indicator of tumors, but also as one of the essential characteristics of cancer [6, 7]. A number of lines of evidence, including dysregulated TCA (Krebs/Citrate)-cycle progression and the insufficient oxidative phosphorylation in cancer cells, suggest that mitochondrial dysfunction might precede the metabolic change [8]. Thus, "cancer must be a mitochondrial disease". In this chapter, which focuses on the causative factors that lead to mitochondrial dysfunction, we discuss whether "cancer is a transcriptional disease". Most of the genes (99%) that encode mitochondria or their function-associated proteins are contained in nuclear genomes [9]. The mitochondrial functions might be recovered or improved at a transcriptional level. In this chapter, we propose the establishment of novel chemo-/gene-therapies with no side effects, to force cancerous cells to regenerate into their normal differentiated state.

2. The relevance of duplicated GGAA-motifs in the 5′-upstream regions of human genes to the regulation of biological events

2.1. The transcription factors that recognize and bind to the GGAA-containing motifs

The most widely known transcription factors (TFs) that selectively recognize the GGAA-core-containing sequences are the ETS (E26 transformation specific) family proteins, which consist of at least 27 members [10, 11]. Moreover, a genome-wide ChIP-seq analysis estimated that the promoter regions of human genes are very frequently occupied by ETS family or GGAA-binding proteins [12]. The duplication of the GGAA-motif could be advantageous to organisms, as it would allow the transcription of various genes to be controlled in a manner that is mainly dependent on the expression profile of the GGAA-binding proteins in the cells [13, 14]. Besides ETS family proteins, several TFs could bind to the motif. For example, some of the duplicated GGAA-motifs would be identical to IFN-stimulated response element (ISRE), the consensus sequence of which is 5′-GGAAANNGAAACT-3′ [15], if one of the Ns was G. The double-stranded sequence, 5′-AACTTT-3′, which is a core binding motif of the IRF1 [16], could be generated if CT was inserted between GGAA and TTCC. Moreover, NF-κB p65 (RELA) homodimer binds to two symmetric sequences, 5′-GGAATTTCC-3′ and 5′-GGAATTCCC-3′ [17]. IRF8 (ICSBP) either positively or negatively regulates transcription through binding to ISRE [18, 19].

Importantly, the ETS family proteins and other TFs cooperatively regulate the expression of various genes. For instance, STAT1 plays a role in the regulation of the expression of interferon (IFN)-stimulated genes (ISGs) with ETS family proteins [20, 21]. Sp1 and Ets1 interact with each other to regulate mouse *Npr1* gene expression [22]. The ETS-binding consensus sequence is frequently found with a second ETS-binding sequence and with the Sp1-binding sequence, but not with a TATA element [23], implying the exclusive role of the GGAA- and TATA elements. The human

VEGFR1 promoter region, which contains overlapping GGAA-motifs, is also regulated by CREB and EGR-binding elements [24]. Furthermore, the mouse *Ppp2r1a* gene promoter, which carries duplicated TTCC motifs, is regulated by Creb, Ets1, Ap2 alpha, and Sp1proteins [25]. Thus, multiple elements adjacent to duplicated GGAA-motifs may recruit various TFs to form a pre-initiation complex on the transcription start site (TSS) of TATA-less promoters. The transcription initiation system might be advantageous for a rapid response to stresses in a TATA-independent manner.

2.2. The duplicated GGAA-motifs that are contained in the 5′-upstream regions of immune response factor-encoding human genes

Duplicated GGAA-motifs are found in the 5′-upstream of the ISGs [20, 26, 27]. The GGAA-motifs are also harbored in the IFN-stimulated response element (ISRE)-like sequences [28, 29]. Thus, the duplicated GGAA-motifs near TSSs may play roles in controlling the expression of ISGs. The ISG-encoded proteins include TFs, immune modulators, apoptosis mediators, and anti-viral factors [30]. Previously, the duplicated GGAA-motifs in the regulatory regions of ISGs have been analyzed [31]. We surveyed the 5′-upstream regions in a number of ISGs to find GGAA-motifs within 500-bp upstream from the TSSs [32], and reported that IFNβ-inducible human *OAS1* promoter activity is regulated by binding of ELF-1 (which belongs to the ETS family proteins) to a duplicated GGAA-motif, and by its interaction with Sp1 and Rb proteins [33].

Collectively, the majority of the promoter regions from ISGs contain duplicated GGAA-motifs but rarely with TATA element. This suggests that the mechanism by which transcription is initiated differs from that of the house-keeping genes or genes that are essentially required, such as those that encode cell structure components. IFNs, the expression of which should be suppressed under normal conditions, only play important roles when it is necessary to fight against viral infection and oncogenesis. The duplicated GGAA-motifs might have contributed, through evolution, to the development of an immune response at the transcriptional level. In addition, GGAA-binding factors, which are associated with other TFs around TSSs, facilitate the expression of each ISG as appropriate, depending on the different signals that are induced by IFN.

2.3. The duplicated GGAA-motifs in the 5′-upstream regions of the human DNA repair factor-encoding genes

The duplicated GGAA (TTCC) motif is present adjacent to the TSS of the human *TP53* gene [34], the expression of which is regulated by IFN-α and β [35]. IRF1 was reported to be a negative regulator of the human *TERT* promoter in response to IFN-γ [36]. In addition, IRF-5 has been shown to upregulate the expression of DNA repair/apoptosis-associated genes [37]. Moreover, DNA damage initiates an immune response that regulates DNA repair-associated genes [38]. These observations suggest that the immune responses and DNA damage responses might be co-dependent, and that the duplicated GGAA-motifs have important roles in controlling the expression of genes that encode DNA repair-associated factors in response to IFN-induced signals.

It should be noted that the duplicated GGAA-motif is present in the promoter regions of the human *Poly(ADP-ribose) polymerase 1*(*PARP1*) [39, 40] and *XRCC1* [41] genes. The duplicated GGAA-motifs are present near the TSS of the *ADPRHL2* (*ARH3*) and the *ZC3HAV1* genes,

which encode mitochondria-localizing poly(ADP-ribose) (PAR) degrading enzyme [42] and an anti-viral RNA-binding protein PARP13 [43, 44], respectively. These findings suggest that the expression of genes encoding single-strand DNA break repair factors is commonly regulated by the duplicated GGAA-motifs.

The promoter activities of the human *WRN* and *TERT* genes, both encoding telomere maintenance factors, positively respond to both 2-deoxy-D-glucose (2DG) [45] and *trans*-resveratrol (Rsv) [46], which are caloric restriction (CR) mimetic drugs that have been shown to prolong the life span of several organisms [47]. The natural compound Rsv upregulates the expression of the *HELB* gene [46, 48], which encodes DNA replication and DNA double strand break repair-helicase HELB (HDHB) [49–52]. Moreover, the 5′-regulatory regions of the genes that encode DNA repair factors, such as *XPB*, *RB1*, *RTEL1*, *ATR*, *TP53*, and *CDKN1A (p21)*, contain GGAA duplications near the TSS [53]. Several of the DNA repair factors are localized in the mitochondria and may also regulate the mitochondrial functions [53].

2.4. The surveillance of regulatory regions adjacent to the TSSs of human mitochondrial function-associated genes

The surveillance of a human genomic DNA database suggested putative TPA-responsive elements in the 5′-upstream regions of the *MRPL32*, *NDUFB3*, *NDUFS3*, *SDHB*, and *SDHAF2* genes contain GGAA duplication [54]. The duplicated GGAA-motifs are present in the upstream regions of human genes encoding mitochondrial ribosomal proteins and enzymes or components that function in the TCA cycle and oxidative phosphorylation (OXPHOS) [54].

Mitochondrial dysfunction is thought to cause either cellular senescence or oncogenesis [55–58]. Remarkably, TCA cycle enzymes, fumarate hydratase (FH), and succinate dehydrogenase (SDH) have been suggested as tumor suppressors [59]. Hence, mutations of the TCA cycle factor-encoding genes give rise to abnormal mitochondrial respiration, which is one of the characteristics of tumors and cancer [60, 61]. Mutations of the *IDH1* and *IDH2* genes have been identified in human brain cancer cells [62, 63]. A recent study demonstrated that the mutation of IDH2 could lead to the generation of sarcoma [64]. Duplicated GGAA-motifs are contained in the upstream region of the *NAMPT* (*NmPRT*), encoding a nicotinamide phosphoribosyltransferase that catalyzes the first rate-limiting step of (nicotinamide adenine dinucleotides) NAD^+ synthesis from nicotinamide [65–67]. Depending on the NAD^+ level, NAMPT could modulate the TCA cycle, poly(ADP-ribosyl)ation, and sirtuin-mediated de-acetylation [66, 67]. The duplicated GGAA-motifs are present near the TSSs of the human TCA cycle enzyme-encoding *ACLY*, *ACO2*, *CS*, *FH*, *IDH1*, *IDH3A*, *IDH3B*, *SDHAF2*, *SDHB*, *SDHD*, and *SUCLG1* genes [68].

A duplicated GGAA-motif is present in the bidirectional promoter of the *PDHX* [54], which encodes one of the components of the PDH enzyme to metabolize pyruvate to acetyl-CoA. Aberrant pyruvate metabolism is thought to play a prominent role in cancer [69]. The genomic deletion of *ME2*, which encodes malic enzyme 2 (an NAD^+-dependent malate decarboxylase that converts malate into pyruvate), is found in pancreatic ductal adenocarcinoma [70]. The GGAA-duplication is not only found near the TSSs of the human *ME2* gene, but

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also the *MDH2* gene (which encodes NAD^+-dependent malate dehydrogenase), suggesting that duplicated GGAA-dependent transcription could affect the metabolism of malate in the mitochondria.

3. The possible roles of metabolic states that can alter transcription profiles

Recently, a study using a CAP-SELEX analysis showed that different transcription factors, such as FOXO1 and ETS family proteins, are mediated by a DNA that contains a GGAA-core motif [71]. As described above, a number of promoters or regulatory regions of human genes that encode immune response-/DNA repair-/mitochondrial function-associated proteins contain overlapping or duplicated GGAA-containing motifs. Thus, the alteration of the profile of the GGAA-motif-binding proteins or their associated protein factors may allow for the control of appropriate cellular responses against viral infection, DNA damage, and oxidative/nutrient/metabolic stress. Importantly, the DNA damage responses affect the transcriptional state [72] through oxidative stress, which is mainly produced by the mitochondria [73, 74]. NF-κB- and p53-dependent transcription, which regulates the expression of the ISGs and DNA repair factor-encoding genes, is also affected by oxidative stress [75]. Thus, metabolites that are mainly produced by respiration or mitochondrial functions may influence the transcription control system [76, 77].

3.1. The transcription profile may be controlled by the NAD^+/NADH balance

We have reported that the promoter regions of the human *TP53*, *HELB*, and telomere maintenance factor-encoding genes respond positively to Rsv [46, 48, 78]. Rsv not only activates SIRT1, which is an NAD^+-dependent deacetylase [79], but also inhibits phosphodiesterase [80]. Importantly, low-dose Rsv activates mitochondrial complex I [81] to upregulate the NAD^+/NADH ratio, to induce the expression of duplicated GGAA-motif-driven genes. The transcription of the bidirectional promoter-driven *BRCA1/NBR2* genes, which contain a duplication of the GGAA-motif, may be regulated by the NAD^+/NADH ratio [82]. Notably, the C terminal-binding protein (CtBP) [83, 84] has a central role in this regulation as a metabolic sensor. Moreover, PARP1 poly(ADP-ribosyl)ates transcription elongation factor NELF to release the paused RNA pol II-dependent transcription [85], suggesting that PARP1 itself contributes to NAD^+-sensitive transcription. Recently, it was reported that nuclear PAR can be utilized by NUDIX5 to supply ATP molecules, which are required for chromatin remodeling [86]. Thus, the accumulation of NAD^+ molecules or NAD^+/NADH ratio-sensitive proteins, including GGAA-motif binding TFs, might affect the transcription of ISGs/DNA repair/mitochondrial function-associated genes in response to metabolic stress.

It should be noted that PARP activity is upregulated in tumors and cancer cells [44]. Because the duplicated GGAA-motifs are present in the 5′-upstream regions of the human *PARP* and *PARG* genes [40], subtle changes in the quality/quantity profile of the GGAA-binding TFs may

modulate the PAR synthesis/degradation ratio at the transcription level. The accumulation of NAD^+ molecules in cells might be transiently caused by mitochondrial dysfunction, which is usually accompanied by insufficient OXPHOS or aberrant respiration [87, 88]. However, when DNA damage eventually activates PARP, NAD^+ molecules will be consumed to synthesize PAR polymer in the nuclei or mitochondria. Thus, the decrease in the NAD^+/NADH ratio would not only reduce the activities but also the expression of enzymes that function in the NAD^+-dependent TCA cycle progression. At this point, cells will have to produce ATP in a mitochondria-independent manner. This metabolic change would be observed as the "Warburg effect" in cancer cells [5, 6].

3.2. The regulation of TFs and nucleotide binding proteins by poly(ADP-ribosyl)ation

PARP inhibitors, such as talazoparib, niraparib, rucaparib, olaparib, and veliparib, are clinically used for the treatment of cancer, especially when *BRCA1* and *BRCA2* gene mutations are present [89]. They all interact with the NAD^+-binding site of the catalytic domain of PARP1 and PARP2. A recent study indicated that the NAD^+-binding pocket of the PARP1 regulates interaction with DBC1, which is deleted in breast cancer 1, which is a known SIRT1 inhibitor protein [90]. A decrease in the NAD^+ will upregulate the interaction between DBC1 and PARP1, leading to the suppression of its activity. This might partly explain why DNA repair declines with aging [91]. The poly(ADP-ribosyl)ation of proteins not only initiates the response to DNA damage, but also regulates the transcription of specific genes [92]. The poly(ADP-ribosyl)ation of C/EBPβ by PARP-1 modulates its transcriptional activity to enhance the expression of the genes encoding factors that regulate adipogenesis [93]. A recent study showed that the poly(ADP-ribosyl)ation of an RNA-binding protein HuR by PARP1 stabilizes *Cxcl2* gene transcripts [94]. Moreover, the poly(ADP-ribosyl)ation of FoxO3 suppresses its transcriptional activity and leads to cardiac hypertrophy [95]. Taken together, poly(ADP-ribosyl)ation, which consumes NAD^+ as a substrate for PAR synthesis, may regulate transcription to respond to DNA damage-induced signals. Thus, it should be noted that PARP inhibitors not only limit the DNA damage response to lead to the death of cancerous cells, but also reduce the consumption of NAD^+ molecules to modulate the transcription of specific genes.

4. Epigenetic alterations in chromosomal DNAs and proteins

Epigenetic alterations are frequently found in cancer, implying that "cancer is an epigenetic disease" [96]. It has been hypothesized that epigenetic and/or transcriptional changes play a role in determining the chromatin state in tumor cells [97]. Epigenetic regulation is mainly driven by modifications of chromosomal DNAs and histone proteins [98]. The biological relevance between cellular metabolites and the gene expression has been proposed as the RNA/enzyme/metabolite (REM) networking system [99]. The metabolites, NAD^+, S-adenosylmethionine (AdoMet), and acetyl-CoA, are the substrates for poly (ADP-ribosyl) ation, methylation, and acetylation, respectively [76], suggesting that these metabolic state-dependent molecules play important roles in the epigenetic regulation.

4.1. The possible functions of poly(ADP-ribosyl)ation on epigenetic regulation

NAD^+ not only plays important roles in DNA repair, mitochondrial functions, and cellular senescence [72, 100], but also affects the modification of chromatin proteins [77] and modulates the gene expression regulatory system [101]. More importantly, NAD^+ is a substrate for the PARP enzyme to synthesize PAR macromolecules, which modify both PARP itself and chromosomal proteins and DNA repair factors [67]. Histones and HMGB (High mobility group box) proteins can be poly(ADP-ribosyl)ated [102–105], suggesting that modifications by such macromolecules on chromosomes affect the epigenetic regulation of the gene expression system. Moreover, poly(ADP-ribosyl)ation on the chromosomal insulator protein CTCF (CCCTC-binding factor) may be involved in epigenetic regulation [106, 107]. Recently, it was shown that CTCF binds directly to PAR to be recruited at DNA lesion sites, indicating that the CTCF also plays a role in the DNA damage response [108]. It has been suggested that poly(ADP-ribosyl)ation affects the methylation patterns in chromosomal DNAs [109, 110]. A recent study showed that the transcriptional regulation of the *EZH2* gene, which encodes the catalytic subunit of the polycomb repressive complex 2 (PRC2), by PARP1 [111], affects the methylation of chromatin proteins [112]. Because the incidence of cancer increases with aging [113], a decline in the cellular level of NAD^+, which might accompany the decrease in PARP activity [114]. SIRT1, which depends on the NAD^+ molecule to de-acetylate histone proteins, plays important roles in the aging process [115]. Taken together, these observations imply that NAD^+ and its polymerized form, PAR, are involved in epigenetic regulation, and that it may be altered in line with the aging process.

4.2. The DNA methylation of chromosomal DNAs

The methylation of promoter regions of specific genes in human chromosomes can be used as biomarkers in various cancers [116]. The DNA methylation reaction is catalyzed by methyltransferases (DNMTs), which utilize AdoMet as a methyl group donor [117]. A recent study showed that intragenic DNA methylation, which is carried out by Dnmt3b in mouse embryonic stem cells, protects the gene body from the entry of spurious RNA pol II and the initiation of cryptic transcription [118]. The extended data showed that the ETS factor binding regions are sensitive to the knock out of the *Dnmt3b* gene, suggesting that the occupation of the GGAA (TTCC)-motifs by GGAA-motif binding proteins could be epigenetically controlled by methylation. Furthermore, the regulation of demethylation by ten-eleven translocation (TET)-family enzymes [119], the activity of which is reduced by hypoxia, should not be ignored. Hypoxia-induced hyper methylation has been demonstrated to occur on the promoter regions of the DNA repair factor-encoding genes, including *BRCA1*, *FANCD2*, *FANCF*, *POLL*, and *UNG* [120]. Of note, the duplicated GGAA-motifs are contained in these gene promoters [53]. A methylation sensitive SELEX analysis showed that ETS-binding was inhibited by mCpG, though NFAT, which also recognizes the GGAA-core motif sequence and preferentially binds to methylated DNA [121]. The observation suggests that GGAA-motif recognizing TFs could be classified into two groups according to their preference to DNA methylation.

The SET protein is an epigenetic regulatory factor that promotes loss of methylation through direct interaction with hypo-acetylated histones [122]. A genome-wide analysis showed that DNA hypermethylation is apparently induced in old male adults, relative to young male

adults, suggesting a relationship between DNA methylation and aging [123–125]. Moreover, the methylation and demethylation of the lysine residues of histones might affect the regulation of transcription [126]. In summary, AdoMet, a methyl group donor, plays an important role in epigenetic control.

4.3. The acetylation of histones could regulate the generation or progression of cancers

Acetyl-CoA is required for acetylation on the lysine residue of histones [127]. This process is catalyzed by acetyltransferases (HATs), including KAT2A (GCN5), KAT2B (CAF), KAT5 (ESA1), KAT7 (HBO1), and KAT8 (MOF) [128], which can be classified into two major groups: the GCNT and MYST families [129]. At least 11 enzymes are known to be histone deacetylases (HDACs) [130]. Because the increased or aberrant expression of HDACs has been reported in various cancers, inhibitors or modulators of HDACs are expected to be effective as anticancer drugs [131]. On the other hand, the lysine acetylation is negatively regulated by sirtuin proteins, including SIRT1 [116], which de-acetylate proteins, utilizing NAD^+ as an acceptor of the acetyl group [127]. It is hypothesized that a reduction in nutrient levels could induce the accumulation of NAD^+ to activate sirtuins. Histone de-acetylation is consistent with the finding that CR mimetics prolong the life span [131–133]. In cancer cells, if mitochondrial dysfunction occurs with a reduction in the NAD^+ level or the hindrance of the progression of the TCA cycle, acetyl-CoA might only be converted to citrate to be used as an acetyl group donor for histones in the nuclei. If so, an increase in histone acetylation would occur naturally in the course of oncogenesis. The activation of HDACs in cancer cells might be the response to the aberrant hyper-acetylation of histone proteins that could lead to the abnormal transcription of various genes, including the mitochondrial function-associated genes.

To summarize, key metabolites, NAD^+ and acetyl-CoA could regulate DNA methylation and histone acetylation directly or indirectly, and play essential roles in epigenetic control.

5. Mitonuclear communication regulates apoptosis, DNA repair, and aging

The mechanisms by which nuclear DNA damage signaling causes the mitochondrial dysfunctions that accelerate aging and aging-related diseases including cancer have been investigated in a review [134]. This process can be referred to as "mitonuclear communication" [135], suggesting that DNA repair systems are integrated into the mitochondrial functions. Given that α proteobacteria are the putative ancestors of the mitochondria [136], they need to take care of the nuclear DNAs that contain almost all (99%) of their essential protein-encoding genes [9]. Thus, the mitochondria might have developed a nuclear genome monitoring system, especially when DNA damage is induced. Several TCA cycles or metabolic enzymes functions as tumor suppressors [59, 64, 137], suggesting that mitochondrial dysfunction may lead to cancerous states.

5.1. The mitochondria play the role of judge in the decision to induce cell death

The execution of apoptosis is mediated by the mitochondria in response to various stresses, including DNA damage and immunological stress signals [138–140]. Thus, the mitochondria

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are known to serve as master regulators of danger signaling to determine cell death or survival [141]. Several mechanisms, including the regulation of the regulators of apoptosis [142, 143] and miRNAs [144], are involved in the induction of apoptosis. The surveillance of the human genomic DNA database indicated the presence of the duplicated GGAA-motifs in the 5′-regulatory regions of the human *PDCD1*, *DFFA*, *BCL2*, *FAS*, *FASL*, *ATG12*/*AP3S1*, *APOPT1*/*BAG5*, and *HTRA2*/*AUP1* genes [13, 53, 54]. These observations suggest that the expression of the apoptosis regulating factor-encoding genes is modulated by the GGAA-duplicated sequences. In this context, apoptosis or programmed cell death, which is controlled by the mitochondria, partly depends on the GGAA-motif binding TFs.

5.2. The localization of p53 and other DNA repair factors in the mitochondria and the regulation of their gene expression

Recent studies have shown that the p53 protein not only acts as a "guardian of the genome", but also serves as a regulator of metabolism [145, 146]. Moreover, p53 has been reported to accumulate in the mitochondria in response to stress [147]. Besides p53, a number of widely known DNA repair factors, including ATM, BRCA1, PARP, PARG, and RB, localize in the mitochondria or regulate their functions [148–152]. The surveillance of the 5′-upstream regions of these DNA repair factor-encoding genes revealed that they commonly possess duplicated GGAA-motifs [53, 78].

GGAA-motif duplications are found in the bidirectional *APEX1*/*OSGEP* promoter region. The *APEX1* encodes apurinic/apyrimidinic endonuclease 1 (APE1) that regulates both the base excision repair (BER) and the mitochondrial DNA repair systems [75, 153]. The GGAA-duplication is contained in the regulatory region of the head–head configured *ACO2*/*PHF5A* genes [54]. The *ACO2* gene encodes aconitase, which plays an important role in the TCA cycle to produce citrate and isocitrate, and which also serves as a mitochondrial redox-sensor [154]. Importantly, aconitase and mitochondrial BER enzyme OGG1 (8-oxoguanine DNA glycosylase) cooperatively preserve mitochondrial DNA integrity [155]. We also confirmed that the duplicated GGAA-motifs were present in the 5′-upstream regions of the genes associated with Fanconi's anemia (FA) [53], which encode the DNA repair factors that are shown to regulate nucleotide excision repair and genome stability [156]. Interestingly, it was shown that mitochondrial dysfunction forces FA cells to produce energy by glycolysis [157], suggesting that FA proteins might be involved in the metabolic switch system in cancer cells. Additionally, Cockayne syndrome proteins CSA and CSB, which play roles in nucleotide excision repair (NER), accumulate in the mitochondria under oxidative stress [158]. In KRAS/LKB1-mutant lung cancer cells, carbamoyl phosphate synthetase-1 (CPS1), which is localized in mitochondria and which eliminates NH_4 to initiate the urea cycle, also plays a role in controlling the pyrimidine/purine balance to regulate the integrity of nuclear DNAs [159]. In this circumstance, the silencing of the *CPS1* gene expression leads to an incomplete S-phase or apoptotic cell death due to increased DNA damage. As expected, the duplicated GGAA is present in the *CPS1*/*LANCL1* bidirectional promoter region. However, no such element is found near the TSSs of either the *CAD* or *ASS1* genes, which encode cytoplasmic enzymes carbamoyl phosphate syntetase-2 and argininosuccinate synthase, respectively. These observations suggest that expression of the mitochondria-localizing, DNA repair-associated protein-encoding genes could be cooperatively regulated by duplicated GGAA-motif binding TFs, supporting the hypothesis that mitochondrial dysfunction causes oncogenesis [8].

5.3. The communication between telomeres and mitochondria may depend on the NAD+/ NADH ratio

The telomeres and mitochondria are thought to communicate with each other [160]. Several nuclear DNA repair factors play roles in the maintenance of mtDNAs, and damaged mtDNAs in turn exert signals to regulate nuclear transcription [74]. The system by which DNA repair/energy production is monitored might be mediated by the balance of the NAD+/NADH ratio, which is regulated by a number of enzymes in the nuclei, mitochondria, and cytosol [161]. In breast cancer cells, the crosstalk between BRCA1 and PARP1 maintains the stability of the DNA repair ability, which would be partly sensitive to the NAD+ concentration [162].

The mitochondria might have conveniently deposited their function-associated genes into the nuclei, but need to take care, especially when DNA damage occurs. However, high-dose or repeated DNA damage may eventually activate the PARP enzyme, which consumes NAD+ as a substrate for the synthesis of PAR, to initiate the DNA repair system [66]. The decrease in the NAD+ level will subsequently cause incomplete TCA cycle progression and the dysregulation of respiration/OXPHOS, accompanied by the reduced expression of the mitochondrial function-associated genes. At this stage, the "Warburg effect" can be observed (**Figure 1**).

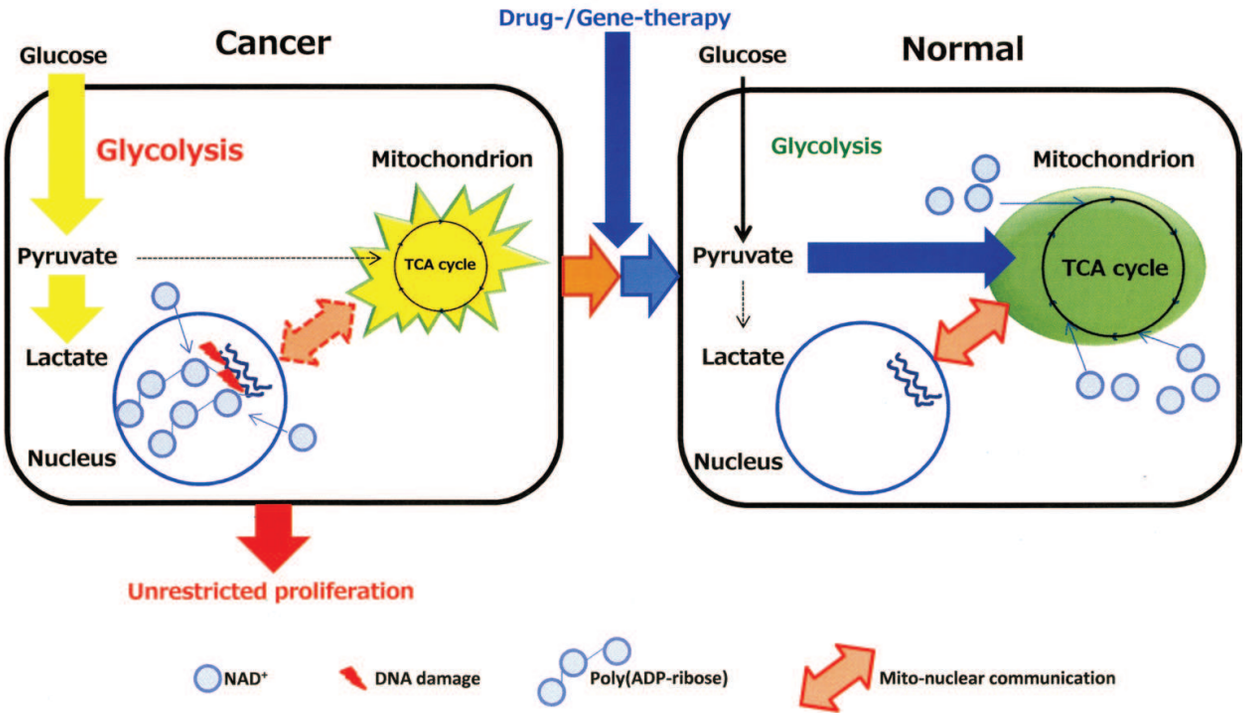

Figure 1. Toward the establishment of a novel cancer therapy. Cellular NAD+ molecules will decrease in accordance with aging or increased levels of various types of stress, especially DNA damage, which activates the PARP enzyme, which synthesizes PAR to consume NAD+ as a substrate. Subsequently, alterations in the transcriptional profile might occur, leading to a reduction or the mismanagement of the mitochondrial functions. In these circumstances, energy producing mitochondrial respiratory systems will decline or be dysregulated, while glycolysis will be enhanced providing ATP molecules that allow cells to proliferate in an unrestricted manner. Novel cancer therapies should be based on the concept that they will never kill cancer cells; rather, they should force the cells to regain their normal respiratory systems, including the TCA cycle and OXPHOS. The recovery of these mitochondria might also lead to the restoration of the mitonuclear communication system. In order to establish a gene therapy, it is necessary to reveal the molecular mechanisms that control the transcription of the mitochondrial function-associated genes.

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6. The involvement of nicotinamide adenine dinucleotide (NAD^+) in oncogenesis and the aging process

The biological relevance of the NAD^+ molecule, especially in relation to its pivotal roles in metabolism and the protection of chromosomal DNAs, has been discussed in detail [66, 67]. A recent study showed that nuclear PAR can be utilized by NUDIX5 to supply ATP molecules, which are required for chromatin remodeling [86]. Moreover, NAD^+ and its precursor nicotinamide have been reported to ameliorate metabolism or the mitochondrial functions [163–165]. The repletion of NAD^+ improves the mitochondrial functions to prolong the life span of adult mouse stem cells [166]. Conversely, decreased concentrations of NAD^+ could cause aging or aging-related diseases [75]. These observations suggest that the NAD^+ level may be correlated with mitohormesis [167], and that nutrient sensing molecules may control aging [57].

6.1. NAD^+ restricts the generation and development of cancer by supporting the mitochondrial functions

Several drugs that induce an increase in the intracellular NAD^+ level are expected to contribute to the establishment of novel therapeutics for treating age-related diseases, including cancer [168]. Mitochondrial dysfunction has been suggested to be associated with the development of tumors or cancerous cells [169, 170]. In breast cancer cells, the knockdown of the subunit NDUFV1 leads to an aberration in complex I, which was shown to enhance aggressiveness or metastasis [171]. An increase in the cellular level of NAD^+ may be associated with the improvement of the mitochondrial integrity to suppress oncogenesis. PGC-1α, which upregulates mitochondrial biogenesis, drives NAD^+ biosynthesis and thereby induces stress resistance [172]. A recent study showed that PGC-1α suppresses the metastasis of melanoma, acting on the transcription program, namely the PGC-1α-ID2-TCF-integrin axis [173].

A loss of CSB, which can localize in the mitochondria [158], activates PARP1 to synthesize PAR [174], suggesting that the dysregulation of the mitochondrial functions to regulate DNA repair system may reduce the NAD^+/NADH molecular ratio.

6.2. NAD^+-dependent transcription of DNA repair factor-encoding genes

It is worth noting again that the NAD^+ molecule is the substrate for the PARP enzyme, which is required for the DNA damage response and the DNA repair system [66, 67]. The inhibition of the PARP1 enzyme ameliorates the mitochondrial metabolism through the activation of SIRT1 [175]. Conversely, the over-activation of the PARP1 enzyme can lead to mitochondrial dysfunction [176]. The *PARP1* gene expression was found to be negatively regulated when poly(ADP-ribose) glycohydrolase (PARG) siRNAs were introduced into HeLa S3 cells [40], suggesting that the degradation of the PAR macromolecule is required for the transcription of the *PARP1* gene. Because the 5′-upstream regions of both the human *PARP1* and *PARG* genes commonly contain the duplicated GGAA-motifs [53, 54], these two genes may be regulated by an NAD^+-sensitive mechanism. The results support the concept that PARP1 is involved in the NAD^+-sensitive transcription system [85]. In summary, the NAD^+/NADH ratio not only contributes to the DNA repair, but also to the fine-tuning of the transcription of genes that encode the NAD^+ metabolism-associated DNA repair factors.

As described previously, the promoter regions of a number of genes that encode TCA cycle enzymes and DNA repair factors contain duplicated GGAA (TTCC) motifs [53, 54]. Thus, the fine-tuning of the transcription of mitochondrial function-associated factor- and DNA repair factor-encoding genes would be required for cells to conduct mitochondria in response to DNA damage-inducing stress.

7. The development of novel cancer therapeutics to improve mitochondrial functions

In cancer cells, the mitochondrial functions are downregulated but glycolysis is upregulated [7, 8]. Thus, inhibitors of glycolysis/PDHK1/PARP, which target the metabolic switch in cancer cells, could be effective anti-cancer drugs [59]. In general, glycolysis- or glycolytic pathway-targeting drugs are expected to kill cancer cells specifically. For example, 2-deoxy-D-glucose, cisplatin and 5-FU—which have an inhibitory effect on glycolysis—are used to treat cancer in the clinical setting [177]. However, glycolysis is one of the most essential biological reactions. Thus, glycolysis inhibitors may be harmful or toxic to normal cells. Given that mitochondrial dysfunction is another essential cause of oncogenesis, the improvement of the mitochondria might provide clues that can be used to design innovative next-generation cancer therapies.

7.1. Chemicals that will initiate the recovery of mitochondria

Our previous *in vitro* studies showed that Rsv moderately upregulates the expression of various duplicated GGAA-motif-driven genes, including *TP53* and *HELB* [46, 48, 78]. Given that the increase in the NAD^+/NADH ratio can improve the mitochondrial functions, the introduction of the redox reaction-associated genes may be applied in cancer treatment. PARP inhibitors, which are especially effective for treating cancer with BRCA1 and BRCA2 mutations by disrupting specific types of DNA repair systems, are clinically approved drugs [89]. Another compound is TEMPOL, an antioxidant that has a suppressive effect on tumor cell proliferation [178], which increases the cellular NAD^+ level, supporting the DNA repair system [179, 180]. A number of compounds that target mitochondria have been tested in clinical trials [181]. Tocotrienols and their analogues target mitochondria and the immune system, causing the death of cancer cells [182]. Metformin and rapamycin are also expected to be novel anti-cancer/aging drugs that effectively suppress mTOR signaling [183]. Activators of mTOR, AMPK, and PGC-1α have been shown to have a synergistic effect with PD-1 blockade therapy [184], suggesting that mitochondrial activation can augment the immune response.

7.2. Possible gene-therapies that improve the mitochondrial functions

PGC-1α, which is encoded by the *PPARGC1A* gene, has been shown to be involved in the *de novo* synthesis of the NAD^+ [172]. Recently, it was reported that lactamase β (LACTB) is a multifunctional protein, which suppresses tumors through its effects on the mitochondrial lipid metabolism [185]. LACTB is included in mitochondrial complex I and treatment of fibroblast cells with its siRNA reduces complex I activity [186]. It therefore works as an upregulator

of NAD^+. As expected, multiple duplications of the GGAA-motif are present in the bidirectional promoter region between the *LACTB* (*MRPL56*) gene and the bidirectional partner *LOC107987798*. We confirmed that the duplicated GGAA-motif is present near the TSS of the human *PDSS2* gene, which encodes prenyl-diphosphatase synthase subunit 2, which is a modulator of the complex I–III and II–III [133]. The PDSS2 is required for the integrity of Coenzyme Q (CoQ) or ubiquinone, which can improve the mitochondrial functions [187]. Thus, PDSS2 would be one of the targets for novel anticancer agents [188, 189]. The introduction of the *LbNOX* gene, which encodes bacterial NADH oxidase, into HeLa cells via a lentiviral vector ameliorates the proliferative and metabolic defects caused by the impairment of the electron transport chain (ETC) [190].These lines of evidence suggest that NAD^+ metabolism regulator encoding genes, including *PARP*, *PARG*, and *NAMPT*, as well as the *PPARGC1A*, *LACTB*, *PDSS2*, and *LbNOX* genes, could be applied or targeted in anti-cancer gene therapy.

Alternatively, TF-encoding genes can be applied to anti-cancer therapies that aid in the recovery of mitochondria. First, the transcription modulator CtBP might be artificially controlled to suppress oncogenesis or cancer progression [83, 84]. Second, because duplicated GGAA-motifs are present in the 5′-upstream regions of a number of DNA repair factor- and mitochondrial factor-encoding genes, GGAA-motif binding factors could upregulate the mitochondrial functions at the transcriptional level. Recently, it was reported that mouse Gabp, which is an ETS family protein, is required for mitochondrial biogenesis through the regulation of the *Tfb1m* gene [191], suggesting that a *GABP* expression vector might be designed and constructed for cancer treatment. The 5′-upstream regions of a number of human genes contain the GGAA-duplication, and it is a GC-box that is very frequently found near the GGAA-core motif [12]. Recently, it was reported that mutations on the ETS family protein-encoding *ERF* and *ERG* genes play roles in prostate oncogenesis [192], implying that imbalances in GGAA-binding TFs could lead to aberrant gene expression. In order to determine which TF-encoding genes should be chosen, the mechanisms through which each of these genes is differently regulated during tumorigenesis should be elucidated.

8. Conclusions and future prospects

In this article, we focused on the transcription mechanism that regulates the mitochondrial functions and the DNA repair systems, both of which decline with aging. Although the molecular mechanisms underlying the regulation of the expression of these genes are not yet fully understood, several lines of evidence suggest that it is dependent on the NAD^+/NADH balance.

The anti-cancer drugs that are currently in use, including metabolism inhibitors, telomerase inhibitors, and apoptosis inducers, were developed with the common intention of killing cancer cells. Although immune receptor target drugs have been applied in the clinical setting, they are similar in that they force cancer cells to die. The anti-cancer drugs that are currently in use damage both malignant cancer cells and normal healthy cells. Importantly, the undesired effects of these anti-cancer drugs are problematic with regard to the quality of life (QOL) of cancer patients, especially those who are too old to endure severe adverse effects that occur during the course of chemotherapy. In order to avoid lethal side effects, individual whole

genome sequencing to identify drug sensitivities, the development of a side-effect monitoring system, and the improvement of treatment policies could be adapted. These are the burdens that are necessitated by the intrinsic concept underlying the development and creation of most anti-cancer drugs.

In the near future, novel anti-cancer drugs or therapies must be developed and established. These drugs should not kill cancer cells; rather they should give them a chance to regain the right mitochondrial functions and DNA repair systems, and immunological responses. Natural or chemical compounds can ameliorate the NAD^+/NADH level to improve the mitochondrial functions, DNA repair systems, and even immune responses. Alternatively, specific TF expression vector(s) could be introduced into cancer cells to lead them to recover to a healthy state. A number of promoter regions of the mitochondrial function-, DNA repair-, and anti-viral/tumor factor-encoding genes have duplicated GGAA-motifs with GC-boxes. Needless to say, it is necessary to determine the TFs that should and should not be applied prior to their clinical use. Based on this novel concept, the design of anticancer/tumor drugs or gene transfer vector(s) will contribute to the prevention of aging and its associated diseases, including cancer.

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Abbreviations

CR	caloric restriction
FA	Fanconi's anemia
HDAC	histone deacetylase
IFN	interferon
ISG	interferon-stimulated gene
OXPHOS	oxidative phosphorylation
PAR	poly(ADP-ribose)
PARG	poly(ADP-ribose) glycohydrolase
PARP	poly(ADP-ribose) polymerase
TF	transcription factor
TSS	transcription start site

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