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The effect of *trans*-resveratrol on the expression of the human DNA-repair associated genes

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Abstract

A natural compound Resveratrol (Rsv), which is found in high concentrations in grape skins and red wine, is expected to be a leading drug for elongating the life span and preventing oncogenesis. This compound is reported to have various beneficial effects on health, including the activation of complex I and anti-oxidative stress. We have been focusing on the regulation of the expression of human genes and have analyzed the promoter activities of several genes that encode DNA repair-function-associated protein factors. Notably, the 5'-upstream regions of these genes very frequently contain the duplicated GGAA-motifs that allow HeLa S3 cells to respond to Rsv. In this review, we discuss the molecular mechanism by which Rsv regulates the expression of genes associated with DNA repair. We suggest the possibility of developing new anti-aging/cancer drugs without harmful side effects, based on a new concept of ameliorating or maintaining the cellular NAD^+/NADH level.

Abbreviations: CoQ: Coenzyme Q; CR: calorie restriction; 2-DG: 2-deoxy-D-glucose; HELB: helicase B; IFN: interferon; Luc: luciferase; mtDNA: mitochondrial DNA; NAD: nicotinamide adenine dinucleotide; OXPHOS: oxidative phosphorylation; Rsv: *trans*-resveratrol; TPA: 12-*O*-tetradecanoyl-phorbol-13-acetate; TE: transposable element; TF: transcription factor; UPR^{mt}: mitochondrial unfolded protein response

Introduction

To date, various DNA-repair associated protein factors have been identified and studied. These include DNA polymerases, DNA helicases, and cell cycle regulating proteins. Some of the DNA polymerases are essential for the repair synthesis in damaged parts of the genome [1]. DNA helicases are DNA-binding proteins that have various functions such as unwinding DNA double-strands and changing chromatin structures [2,3]. Several of the cell cycle regulating proteins control the progression of G1/S and play important roles as tumor suppressors, such as the p53[4,5] and RB [6] proteins, which are encoded by the *TP53* and *RB1* genes, respectively. These DNA repair regulatory factors are thought to control cellular senescence, which is suggested to be linked to the maintenance of telomeres [7,8]. For example, mutations of the *WRN* gene, which encodes a Rec Q helicase, are known to cause Werner's syndrome [9]. We previously observed that the expression of the human *TP53* and *WRN* genes (and their promoter activities) is induced in HeLa S3 cells by treatment with *trans*-Resveratrol (Rsv) [10,11], which is a natural compound that is expected to elongate the healthy life span [12,13]. Moreover, Rsv upregulates the expression of the *HELB* gene [10,14], which encodes DNA replication and DNA double strand break repair-helicase HELB (HDHB) [15-18]. Taken together, these observations imply that DNA-repair associated- and DNA/damage response-protein encoding genes are simultaneously regulated, at the transcriptional levels, by Rsv.

In general, the DNA repair and the genome maintenance system are thought to be tightly linked with the cellular aging process and oncogenesis [19, 20]. A recent analysis of the human cancer genome revealed a number of cancer-driver genes, including *TP53* and *RB1* [21,22]. The incidence of cancer in humans increases exponentially with age, suggesting that aging is the strongest demographic risk factor for most human malignancies [23,24]. The investigation of the molecular mechanisms involved in the genome maintenance system, which is affected by Rsv—a natural compound that has health benefits—will be very important in the development of anti-aging/cancer drugs. In this review article, we re-examine the 5'-flanking regions of the human genes that encode the DNA-repair factors and discuss the mechanisms underlying the response to Rsv.

Surveillance of the 5'-flanking regions of the human DNA repair-, interferon response-, and mitochondrial function-associated genes

Transcription is the fundamental biological process through which mRNAs are synthesized for translation into proteins. In eukaryotic cells, the formation of a pre-initiation complex, recruiting RNA polymerase II (RNA pol II) near a TATA-box, is believed to be the most essential factor for the initiation of transcription [25]. However, it is estimated that TATA-less promoters account for 76% of the upstream region of human genes [26]. We reported that 81% of the promoters, which contain no obvious consensus TATA-box sequences, have at least one duplicated 14-bp with GGAA (TTCC) core motif within the 500-bp upstream region [27]. The GGAA

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motif-containing sequences are recognized and bound by the ETS family proteins and other transcription factors (TFs) [28-30]. For example, it has been shown that ETS family protein ELF-1 binds to the duplicated GGAA motifs to regulate the expression of the antiviral *OAS1*, which belongs to the interferon-stimulated genes (ISGs) [31]. Recently, Chuong *et al.* showed—using a ChIP-seq analysis—that STAT1 binds to the interferon-γ (IFNG) activated sequences (GAS), 5'-TTCCGGGAA-3' and 5'-TTCCTGGAA-3', in the MER41B LTR consensus sequence in IFNG-stimulated HeLa cells, suggesting that STAT1 plays an important role in the innate immunological responses [32]. The results were very interesting as they imply that ancestral retroviruses helped to confer the activation system in which transcription is activated upon IFN stimulation. Moreover, interferon regulatory factors (IRFs) can also recognize and bind to the interferon-stimulated response element (ISRE) or the GAS [33]. A recent study showed that the antiviral innate immune response, which is mediated by the TFAM-cGAS-STING-IRF3 signaling pathway, is primarily caused by mitochondrial DNA (mtDNA) stress through viral infection [34]. These observations suggest that the STAT and IRF protein factors are involved in transcriptional regulation through the duplicated GGAA (TTCC) motifs. The competitive binding of different GGAA-motif binding proteins to the same or the adjacent GGAA sequence means that the genetic expression is suitably adjusted by the expression profile of the GGAA-binding proteins in the cells [27]. Further surveillance of the 5'-upstream regions of DNA repair-, interferon response-, and mitochondrial function-associated genes revealed that their expression regulatory regions contain duplicated GGAA motifs near the transcription start sites [35-37]. The observations imply that some of the essential characteristics of cancer, including the DNA damage response and mutations, inflammation, and failure in the mitochondrial respiratory system, could be caused by changes in the profile of the GGAA (TTCC)-binding TFs [38]. Of note, GABP (NRF2), which belongs to the ETS family, is required for mitochondrial biogenesis [39]. A number of cancer causative stresses, including DNA damage responses, are thought to be tightly linked with the aging process [19, 40, 41]. Thus, the establishment of a method to prevent cancer with the use of drugs or gene expression enhancing/inhibiting vectors would also have clinical application in the prevention of aging-related diseases.

The causative role of Rsv in regulating the cellular NAD^+ level to affect transcription and mitochondrial integrity

It was previously shown that the promoter activities of the human telomere maintenance factor-encoding genes positively respond to Rsv [10,42]. Moreover, our recent study showed that the expression of the human *TP53* and *HELB* genes is upregulated by Rsv in HeLa S3 cells, and indicated that they are under the control of the duplicated GGAA (TTCC) motifs, which are contained in their 5'-upstream regions [11,14]. Rsv, which is a natural compound that is contained in red wine, grape skins, and peanuts, not only elongates the life span and health span of various species [43], but is also expected to be a lead compound with anti-cancer/tumor effects [44,45]. Rsv affects a number of biologically-significant proteins, including sirtuins [46], cAMP phosphodiesterase [47], mitochondrial complex I [48], DEPTOR [49], COX-1 and -2 [50], to extend the lifespan [43].

The most essential effect of the Rsv is that it activates SIRT1, which is an NAD^+-dependent deacetylase [12]. The biological relevance of the SIRT1/3 has been reviewed and discussed in the context of the multiple effectors that regulate PGC-1α, FoxO and other functional proteins [51]. The excessive production of the NAD^+ molecule by the Rsv-activated mitochondrial complex I will upregulate the NAD^+/NADH ratio to lead to the modification of chromatin-associating proteins [52] and modulate the gene expression in immune system [53]. It has been shown that the transcription of the bidirectional promoter-driven *BRCA1/NBR2* genes is regulated by the metabolic switch, depending on the NAD^+/NADH ratio, which could be elevated by CR mimetic drugs [54]. It was shown that the C terminal-binding protein (CtBP) [55,56] has a central role in this regulation as a metabolic sensor. The accumulated NAD^+ molecule will be consumed by poly(ADP-ribose) polymerase (PARP) to induce the poly(ADP-ribosyl)ation of nuclear proteins, which is essential for DNA-repair synthesis and the regulation of the telomere length [57,58]. The binding of Rsv to a human tRNA synthetase (TyrRS) leads to activation of PARP1 to induce a stress response [59]. We previously reviewed the biological relevance of the NAD^+ molecule, especially in relation to its pivotal roles in metabolism and the protection of chromosomal DNAs [60,61]. Recently, it was reported that nuclear poly(ADP-ribose) could be utilized by NUDIX5 to supply ATP molecules, which are required for chromatin remodeling [62]. Thus, Rsv might directly or indirectly evoke the DNA-repair system, leading to the accumulation of NAD^+ molecules or the activation of the GGAA-motif binding TFs that are sensitive to the NAD^+/NADH ratio. NAD^+ and its precursor nicotinamide have been reported to ameliorate metabolism or the mitochondrial functions [63-65]. Recently, it was revealed that NAD^+ repletion improves the mitochondrial function to enhance the life span of adult mouse stem cells [66]. Conversely, decreased concentrations of NAD^+ could cause aging or aging-related diseases [67]. These observations are consistent with a number of reports that suggest that Rsv is beneficial for cells inducing NAD^+ level. This effect of the Rsv might be associated with the induction of mitohormesis [68,69].

It has been suggested that mitochondrial dysfunction leads to the development of tumors or cancerous cells [70,71]. 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 [72]. The upregulation of the cellular NAD^+ level, which could be induced by Rsv, may contribute to mitochondrial integrity to suppress oncogenesis. It has been shown that Rsv upregulates mitochondrial biogenesis by the activation of Sirt1-induced PGC-1α [73]. Moreover, PGC-1α has been shown to drive NAD^+ biosynthesis and thereby induce stress resistance [74]. However, Rsv might reduce the level of sirtuin(s), especially when it was used for a prolonged period or at high doses [14,75], suggesting that negative feedback system could regulate the excessive sirtuin activity.

It is worth noting again that the NAD^+ molecule is the substrate of the PARP enzyme, which is required for the DNA damage response and the DNA repair system [60]. PARP1 activation may induce mitochondrial dysfunction [76]. Conversely, the inhibition of the PARP1 enzyme ameliorates the mitochondrial metabolism through the activation of SIRT1 [77]. We observed that the expression of the *PARP* gene was negatively regulated when poly(ADP-ribose) glycohydrolase (PARG) siRNAs were introduced into HeLa S3 cells [78]. As expected, the 5'-upstream regions of both the human *PARP1* and *PARG* genes commonly contain the duplicated GGAA-motifs [37]. Additionally, PARP1 targets and poly(ADP-risosyl)ates transcription elongation factor NELF to release the paused RNA pol II dependent transcription [79], suggesting that PARP1 itself contributes to NAD^+-sensitive transcription. These observations imply that the NAD^+/NADH ratio might contribute to the fine-tuning of the transcription of genes that

encode NAD^+ metabolism-associated DNA repair factors. In other words, an NAD^+-dependent transcription controlling system, which might be regulated by metabolic switch TFs, including CtBP1, CtBP2 [54-56] and PARP1, is required for cells to regulate the mitochondrial function in response to DNA-damage induced stress.

Duplicated GGAA-motifs, GC-boxes and other *cis*-elements that respond to Rsv

Besides the NAD^+-dependent/-sensitive gene expression system, Rsv could affect other TFs. GC-boxes are found in the 5'-flanking regions of the human *TERT* and *WRN* genes [42,80], the promoter activities of which are augmented by treatment with 2-deoxy-D-glucose (2DG) or Rsv in HeLa S3 cells [10,81]. GC-boxes, which are mainly recognized by transcription factor Sp1 [82], are commonly contained in the promoter regions of genes that encode shelterins, which play a part in the maintenance of telomeres [83]. The human *SIRT1* promoter, which contains GC-boxes, positively responds to PPARδ, suggesting that the mitochondrial β-oxidation pathway regulates the transcription of genes whose promoters possess GC-boxes [84]. We recently reported the co-operative function of the GC-boxes with a duplicated GGAA-motif in the human *HELB* promoter region [14]. The 263-bp region of the human *eNOS* promoter, containing binding elements for Sp1and ETS family protein ELF1, responds to Rsv [85]. The co-location of GC-boxes and c-ETS binding elements has been identified in in the 5'-flanking regions of the human *VE-cadherin* (*CDH5*) [86] and *presenilin 1* (*PS1*) genes [87]. Furthermore, an interaction between Sp1 and ETS-1 activates the promoter activity of the murine guanylyl cyclase/natriuretic peptide receptor-A-encoding gene, *Npr1* [88]. The adjacent locations of the ETS-binding motif and GC-boxes are found in a number of human gene regulatory regions [30], suggesting that these genes are ready to respond to Rsv or other mitohormesis-inducing compounds. The nuclear respiratory factor 1 (NRF1) is a DNA binding protein, the consensus binding sequence of which is 5'-YGCGCAYGCGCR-3', binds to the transcriptionally regulatory regions of the mitochondrial function-associated genes in human glioblastoma cells [89]. Several of the NRF1-traget promoters, including the *ATM*, *BAG1*, *COX15*, *FANCL*, *PRKDC*, *SDHB*, *SDHD*, *HARS* and *WRN* genes, commonly contain the duplicated GGAA (TTCC) sequences [36,37]. In a recent study, a CAP-SELEX analysis indicated that TF-pairs are very frequently (95%) mediated/facilitated by DNA [90]. Moreover, it was indicated that the binding sequences for two varieties of TF pairs contain GGAA, and that the binding sites for FOXO1 and ETS family proteins can be closely positioned [90]. FOXO1, which is one of the forkhead box family proteins, regulates the growth of the vascular endothelium cells by reducing glycolysis and mitochondrial respiration [91]. Seventy-three MYC signature genes are downregulated by the forced expression of the gain of function mutation of FOXO1. Among them, GGAA duplications are harbored within 500-bp from the most upstream regions of at least 10 genes *APEX1*, *HSPD1/HSPE1*, *NBN*, *NPM1*, *TP53*, *RFC2*, *RPL22*, *TK1*, and *TYMS*, suggesting that FOXO1 might negatively modulate the transcription of duplicated GGAA-containing promoter driven genes. Thus, the interaction or co-operation between GGAA-binding proteins and other TFs, including Sp1 and FOXO1, might play an important part in the positive or negative response to Rsv. In addition to the ETS family, which includes at least 27 member proteins [92], NF-κB/c-Rel, IRFs, TEAD4, and STATs, have also been shown to bind to the GGAA(TTCC)-core motif containing sequences [32-35,90]. A recent study showed that Rsv enhances the immune function, including the production of IL2, by activating NF-κB in immunosuppressed mice [93]. Rsv induces the binding of EGR1 and EGR3 to the promoter region of the *SMPD1* gene to induce its expression in human leukemia and cancer cells [94]. Moreover, Rsv stimulates cyclic AMP response element-dependent gene transcription [95], suggesting that CREB

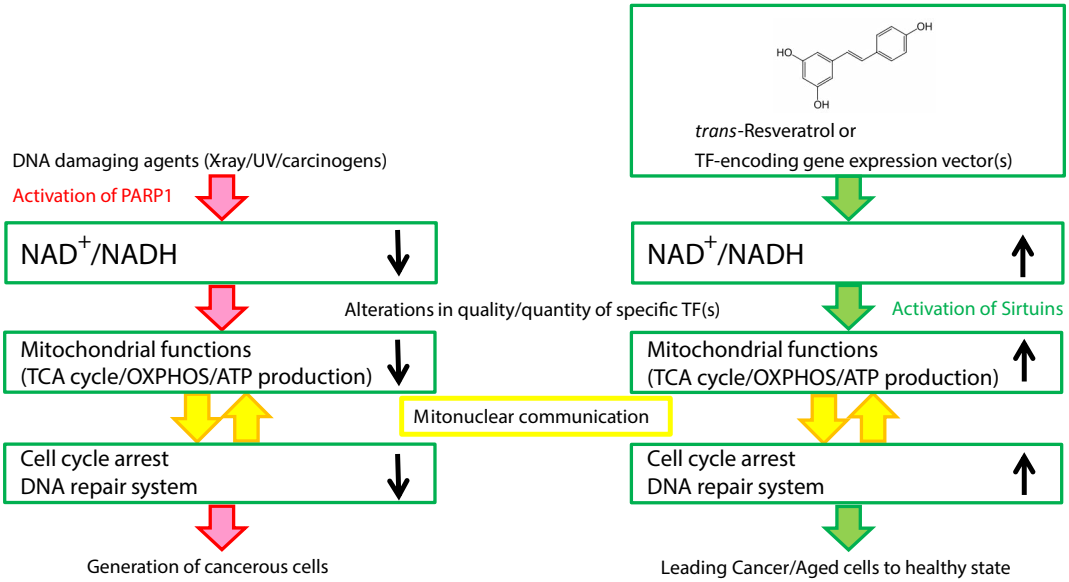

Figure 1. A schematic illustration of the hypothesized mechanism underlying the effects of Rsv or specific TF-encoding gene expression vector(s) on cancer/tumor cells. (Left) DNA damaging agents activate PARP1 to consume NAD^+ for the synthesis of poly(ADP-ribose)s. Although PARP activity is required by the DNA repair system, the persistent reduction in the NAD^+/NADH ratio will impair the progression of the TCA cycle, and the cells will produce ATP by glycolysis, which could be referred to as the "Warburg effect". After the continuous activation of PARP1, cell cycle arrest and the DNA repair system no longer function well, and cells will proliferate regardless of the mitochondrial functions. (Right) Rsv will cause the cells to regain their NAD^+/NADH level and activate sirtuins, NAD^+ dependent transcription, and the mitochondrial functions. The cells will be altered, causing them to depend on the mitochondria, which control the regulation of energy production, cell cycle arrest, and DNA repair or telomeres in an appropriate manner. Rsv would thus directly ameliorate the mitochondria by upregulating the NAD^+/NADH level, and indirectly induce the expression of the mitochondrial function/DNA repair-associated factor encoding genes. Hence, Rsv or some TF-encoding vectors are effective as tumor/aging suppressors.

and ATF2 are the candidate target-TFs for Rsv-induced signals. The downregulation of the phosphorylation of the STAT3/5 proteins by Rsv was reported in human renal carcinoma cell lines [96], suggesting that Rsv negatively regulates STAT3/5-dependent gene expression. Rsv can also downregulate the expression of genes by blocking cytokine-induced NF-κB activation [97], or inhibit the transcription of Snail and thereby reduce its binding to promoter regions [98]. These lines of evidence suggest that Rsv has both positive and negative effects on transcription according to the combination of duplicated GGAA and other *cis*-elements, such as the GC-box, FOXO1, CREB, and NRF1-binding sequences, in the promoter regions.

The epigenetic alterations that are induced by Rsv

It has been suggested that epigenetic alterations in chromosomes play essential roles in the generation and development of cancer cells [99-101]. In addition to NAD^+, S-adenosylmethinine, acetyl-CoA, and other metabolites play important roles in DNA double-strand break (DSB) repair, by modulating chromosomal DNAs and proteins [102]. The aging processes are thought to be controlled by changes in DNA methylation and histone modifications in chromosomes [103-105]. These implications are consistent with the hypothesis that both oncogenesis and the aging process are controlled by both the accumulation of DNA damage [19,106] and by epigenetic alterations [107,108]. Thus, DNA methylation, histone modifications, chromatin organization/remodeling, and the regulation of coding/non-coding RNAs [109], should be taken into account when Rsv or novel anti-cancer drugs are administrated. Because Rsv is a potent activator of sirtuins, which are NAD^+-dependent deacetylases or class III histone deacetylases (HDACs) [110], the alteration of the acetylation of histones and NF-κB [111,112] could be induced by Rsv. A recent study suggested that Rsv enhances the effect of the FoxO1de-acetylation induced by fenofibrate (a SIRT1-upregulating agent), which upregulates the expression of SIRT1 [113]. A similar conclusion was obtained from an *in vivo* experiment, which showed a heart disease-protective effect of Rsv—in its suppression of proapoptotic signaling in the hearts of senescent mice [114]. To date, a number of HDAC inhibitors have been developed as anti-cancer or cancer preventing drugs [115, 116]. However, the regulation by Rsv might be indirect and maybe restricted to the target molecules that are de-acetylated by the sirtuins. The Rsv-induced signals partly affect the nutrient-associated signaling pathway [117], thereby changes in the concentration of the acetyl-CoA molecule may affect the acetylation of nuclear proteins, including histone proteins. Thus, Rsv or sirtuin activators would be novel epigenetic controlling drugs that could have applications in cancer therapy.

The tumor hypoxia-induced inactivation of the TET enzyme, which catalyzes the demethylation of 5-methylcytosine (5mC), causes the hypermethylation of the promoter and enhancer regions of the tumor suppressor encoding genes [118]. Recently, genome-wide surveillance in breast cancer cells showed that both the hyper- and hypo-methylation of cancer-related genes occurred in response to Rsv treatment [119, 120]. In human liver cancer cells, Rsv induced the expression of the *MAT2B* gene, which encodes a methionine adenosyltransferase 2B [121]. Thus, the production of *S*-adenosylmethionine, which is widely known as methyl-group donor molecule, may have an impact on the methylation of chromosomal DNAs. The changes in the microRNA (miRNA) profile of white adipose tissue in response to Rsv treatment were investigated, and the upregulation of triacylglycerol metabolism-associated miRNAs was observed [122]. Among the miRNAs that were upregulated, miR-593-5p had the unique effect of downregulating the expression of SP1 protein, which suggests that Rsv could affect gene expression through the alteration of the cellular miRNA profile. The activities of telomerase and DNA methyltransferase (DNMT) are affected by Rsv treatment, implying that Rsv can induce genome maintenance signals in breast cancer cells [123]. We previously reported that telomerase activity is induced by Rsv in HeLa S3 cells [10]. The relationships between the telomeres and the risks of aging and aging-associated disease risks were reviewed and discussed [124]. Notably, telomere dysfunction compromises the mitochondria, causing them to overproduce reactive oxygen species (ROS) [125]. Thus, telomeres are associated with both the genome maintenance system and in communicating with the mitochondria [126]. Collectively, Rsv-induced signals may spontaneously link with the epigenetic alterations in chromosomes, to regulate the mitochondrial functions.

The effect of Rsv on metabolism and the mitochondria

Various stresses, including oxidative stress and genotoxic stresses, are thought to be the main causes of cellular senescence [127]. Although it is widely believed that cancer is generated from the mutation of oncogenic driver genes, a number of observations, including cell cybrid experiments, strongly suggest that cancer originates from metabolic dysfunctions of the mitochondria [128]. In addition, it has been suggested that aging and neurodegeneration are impaired by mitochondrial deficiency when the dysfunction is mild, but that the effects of mitochondrial deficiency become deleterious when it is severe [129]. Recent studies have shown that Rsv prevents oxidative stresses in pancreatic β cells [130] and in neurons [131]. Rsv not only activates mitochondrial complex I [48] but also AMPK [132,133]. However, Rsv suppresses oxidative stress to prevent the dysfunction of endothelial cells [134]. It should be noted that the mitochondrial unfolded protein response (UPR^{mt}), or a protective mitochondrial stress response, is induced by Rsv [135, 136]. The activation of the UPR may promote longevity and extend the life span [137]. In hematopoietic stem cells, with the help of NRF1, SIRT7 affects the UPR^{mt} -mediated metabolic checkpoint to regulate the aging process, which is defined by the impairment of mitochondrial biogenesis, respiration, and cellular proliferation [138]. Of note, SIRT7 deacetylates GABPβ1, which is a master regulator of the nuclear-encoded mitochondrial function-associated genes [139].

Mitochondrial dysfunction is thought to be one of the reasons for oncogenesis [70, 71, 140]. A germline mutation analysis revealed that several of the TCA-cycle enzyme-encoding genes, including *FH*, *SDHA to D*, and *SDHAF2*, are tumor suppressor genes [141]. The essential role of complex I component NDUFV1 in the progression and metastasis of breast cancer has been shown [72]. Previously, FH (fumarate hydratase) and SDH (succinate dehydrogenase) were suggested to be tumor suppressors [142]. The knockdown of the citrate synthase encoding the *Cs* gene links the Warburg effect to tumor malignancy [143]. The downregulation of the mitochondrial complex 1 to 4- and Krebs cycle-associated gene expression in clear cell renal carcinoma (ccRCC) in comparison to normal kidney tissue was observed in a metabolic RNA-seq analysis [144]. Moreover, a decline in the mitochondrial quality or activity was associated with aging and the related diseases [41]. In this regard, the mitochondria represent the best organelle for directing next generation anti-cancer/aging therapy. Rsv upregulates the mitochondrial mass and ATP production in primary myoblasts [145]. The hypothesis that the mitochondria are the primary target of Rsv-induced signaling is also supported by the surveillance of the genomic sequences of the 5'-upstream regions of the human mitochondrial function-associated genes [36-38].

The results of a gene-wide survey analysis strongly suggest that the ancestor of the eukaryotic cells acquired the original α proteobacteria genome, which may be the origin of mitochondria, through endosymbiotic gene transfer (EGT) [146]. Alternatively, the acquisition of mitochondria, which carry energy production machinery, might have occurred after the incorporation of the genome of other ancestral bacteria [147]. Thus, the mitochondria have their own mtDNAs; however, almost all (99%) of the mitochondrial function-associated genes are present in the nuclear genome [148]. Remarkably, they are under the control of bi-directional promoters that have duplicated GGAA-motifs in common [36]. One possible reason why the mitochondrial function-associated genes are oriented head-head with other protein encoding genes might be that it was advantageous for the ancestral eukaryotes to incorporate bacterial DNAs into the nuclear genome using duplicated GGAA-motifs as landmarks. Actually, the purine-pyrimidine sequences, which are not only identified in the 5'-flanking regions of genes but also in sites involved in recombination, are known to affect the conformation of DNA helices [149]. Thus, duplicated GGAA-motifs might be the traces of the ancient transposable elements (TEs). This is a remarkable topic in the argument on how TFs help in the incorporation of the TEs [150]. The IFNG-responsive *cis*-regulatory elements, including the duplicated GGAA (TTCC) motif containing the GAS sequence, are thought to be remnants of retroviral enhancers [32]. Moreover, recent studies have shown that the binding sites of TFs are highly mutated in cancer cells [151,152]. Thus, an alternative explanation would be that ancestral eukaryotic cells might have acquired exogenous genes preferentially at the duplicated GGAA-motif-containing sites—where nuclear excision repair is impaired—through a long evolutionary process.

We have reported that the duplicated GGAA-motifs in the promoter regions of the human *TP53* [11] and the *HELB* [14] genes play an essential role in the positive response to Rsv in HeLa S3 cells. The results are consistent with a previous study which showed the induction of growth arrest at the S-phase by Rsv in several human cancer cell lines [153]. Given that the duplicated GGAA-motif containing gene promoters could be upregulated by Rsv, the expression of the majority of the mitochondrial function-associated factor encoding genes may be synchronously regulated by Rsv-induced signaling in concert with the genes that encode DNA-repair-associated factors. Rsv may fulfill the stringent criteria for anticipated novel anti-cancer/aging drugs by inhibiting proliferation and improving the mitochondrial functions, to strengthen the DNA-repair system, with considerably fewer undesired side effects in comparison to the anti-cancer drugs that are in current use.

The mitochondrial functions and genome stability: mitonuclear communication stands as a genome maintenance system

The execution of apoptosis is mediated by the mitochondria in response to various stresses including DNA-damage and immunological stress signals [154-156]. Thus, it has been proposed that the mitochondria serve as master regulators of danger signaling to determine cell death or survival [157]. A number of studies have shown that Rsv induces or regulates apoptosis [158]. Several mechanisms, including the regulation of the apoptosis regulators [159, 160] and miRNAs [161], are involved in the induction of apoptosis. On the contrary, Rsv has negative effect on apoptosis by suppressing the NF-κB signaling pathway [162]. The induction or suppression of apoptosis in response to Rsv might be dependent on the concentration or duration of treatment, or the inner cellular protein and RNA profiles. 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*, and *FASL* genes [27]. Moreover, the duplicated GGAA-motifs are contained in bidirectional promoters, such as the *ATG12/AP3S1*, *APOPT1/BAG5*, and *HTRA2/AUP1* gene pairs [36]. Although it has been reported that ETS2 increases apoptosis in the brain and fibroblasts [163,164], the ETS family proteins, which bind to the GGAA (TTCC)-motif-containing sequences, are basically negative apoptosis regulators [39,165]. These observations suggest that the expression of the apoptosis related factor-encoding genes is modulated by the GGAA-duplicated sequences. Hence, genes that encode the executors and modulators of apoptosis are intrinsically upregulated by Rsv at the transcriptional level. However, occasional or temporal signals to induce apoptosis need to be avoided by certain signals that are regulated by the sirtuins, NF-κB and other proteins or miRNAs. Rsv might revoke both the signals that accelerate and decelerate apoptosis at the same time, ultimately bringing the cells to the point that they determine their own fate.

As previously described, the telomeres and mitochondria communicate with each other [126]. Several nuclear DNA-repair factors are suggested to play roles in the maintenance of mtDNAs, and damaged mtDNAs in turn exert signals to regulate nuclear transcription [166]. Recent *in vivo* experiments have shown that the mtDNA haplotype affects the mitochondrial morphology, functions, and aging parameters including the telomere length and UPR^{mt} [167]. 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 [168]. This process can be referred to as "mitonuclear communication" [169]. The nuclear DNA-repair systems need to work efficiently in order to maintain the mitochondrial function. Given that α proteobacteria are the putative ancestors of the mitochondria, the genome size must have been reduced by transferring genes into the ancestral eukaryotic cell nuclei. However, the mitochondria need to take care of the nuclear DNAs that contain almost all of their essential protein-encoding genes. Thus, the mitochondria might have developed a nuclear genome monitoring system, especially when DNA damaging signals are induced. 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 [170]. In breast cancer cells, BRCA1 crosstalks with PARP1 to maintain a stable DNA repair ability, which would be partly sensitive to the NAD^+ concentration [171]. The nucleus could be compared to a bank. We (the mitochondria) can conveniently deposit money (mitochondrial function-associated genes), but need to take care when a financial crisis (DNA damage) occurs. Rsv would represent an alert, that draws our interest toward the bank account.

Toward the development of new concept-based anti-cancer/aging drugs

In cancer cells, glycolysis is upregulated but the TCA cycle is downregulated [70,128]. Thus, inhibitors of glycolysis/PDHK1/PARP could be effective anti-cancer drugs targeting the metabolic switch in cancer cells [172]. It should be noted that Coenzyme Q (CoQ) can improve the mitochondrial functions [173]. *Pdss2* KO mice, which carry complex I-III and II-III dysfunction due to insufficiency of CoQ or ubiquinone, show metabolic alterations and a Parkinson's disease-like phenotype [174]. Defects in CoQ_{10} biosynthesis have been suggested to be one of the possible causes for glomerular or

renal diseases [175]. We confirmed that the duplicated GGAA-motif, 5'-AAAGCTTCCGGGAGGAACTGGT-3', is present near the TSS of the human *PDSS2* gene, which encodes prenyl diphosphatase synthase subunit 2, implying that Rsv indirectly affects CoQ synthesis. These observations suggest that antioxidants, such as CoQ_{10} and vitamins C/E, would be lead drugs for anti-aging-associated disease, including Alzheimer's disease [69,176]. Vitamin E or tocotrienols, and their analogues target mitochondria and the immune system to let cancer cells die [177]. Metformin and rapamycin are also expected to be novel anti-cancer/aging drugs that effectively suppress mTOR signaling [178]. A number of compounds that target mitochondria have been tested in clinical trials [179].

The introduction of gene expression vectors into cells or the editing of the genome of cells would represent an alternative approach to anti-cancer/aging therapy. As described above, Rsv can moderately upregulate the expression of various duplicated GGAA-motif driven genes, including the *TP53* gene, suggesting that the expression vectors of the GGAA-motif binding proteins should be a primary target for examination. Moreover, given that the upregulation of the NAD^+/NADH ratio improves the mitochondrial functions, the introduction of the redox reaction-associated genes could be applied in cancer treatment. The introduction of *LbNOX oxidase* (*LbNOX*) gene expression—which encodes an 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), which is associated with many human diseases [180]. For example, in the near future, skin grafting after the establishment of genome-edited iPS cells or direct gene transfer could be applied to the treatment of skin diseases, including melanoma [181]. The transfer of mitochondria or mtDNA into cells could be another therapeutic strategy for the treatment of mitochondrial dysfunction-related diseases [166,182,183]. If this therapy is applied on oocytes or fertilized eggs, the risk for cancer or aging processes could— in principle—be drastically reduced from birth. However, careful ethical consideration and safe and rigid therapeutic and technological guidelines are required for the handling of these cells.

Concluding remarks

In this article, we mainly focused on the relationships between the mitochondrial functions and the DNA repair systems, and suggested that they could both be controlled by Rsv at the transcriptional level. 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 or ratio.

Anti-cancer drugs that are in current use, including telomerase inhibitors, were developed with the intention of killing cancer cells. Although drugs immune receptor target drugs have been applied in the clinical setting, they are similar in that they attack cancer. Almost all of the anti-cancer drugs induce cell death not only in malignant cancer cells, but also in normal healthy cells. Sometimes the side effects are too severe to be ignored. In order to avoid lethal side effects, individual whole genome sequencing to find sensitivities to drugs, the development of a side effect monitoring system, and the improvement of treatment policies are required. These heavy tasks are necessitated by the intrinsic concept underlying the development and creation of most of the anti-cancer drugs that are in current use.

In the near future, a new concept for anti-cancer drugs or therapies must be developed and established. That is not to kill cancer cells but to force them to convert to a normal healthy state. Natural compounds, such as Rsv, or artificially generated compounds that ameliorate the mitochondrial functions and DNA repair systems to increase the NAD^+/NADH level, are expected. Alternatively, specific TF expression vector(s) could be introduced into cancer cells to bring them back to the healthy state with both mitochondrial and chromosomal integrity. Somatic cells are able to gain pluripotency by the introduction of Yamanaka factors, all of which belong to DNA-binding TF. This implies that cancer/tumor cells could be forced to go back to the healthy state with the help of a TF(s). Designing anti-cancer/tumor drugs or gene transfer vector(s) based on this new concept will contribute to the prevention of aging and its associated diseases, including cancer.

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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