Chapter

Introductory Chapter: Gene Expression Controlling System and Its Application to Medical Sciences

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1. Introduction

We have learned that genes in mammalian cells are transcribed into messenger RNAs (mRNAs), which are to be translated into polypeptides (proteins). This is known as "Central Dogma." Gene expression must be appropriately maintained to regulate development, differentiation, and proliferation of cells. Imbalances or disturbances in gene expression are sometimes deleterious for living things. For example, steroid and thyroid hormones directly bind to nuclear receptors, which induce expression of specific genes. Recent global analyses of gene transcripts revealed that specific transcription factors (TFs) and their networking systems physiologically correspond to the onset of human diseases, including cancer. In other words, expression of specific genes might have relevance to pathogenesis of diseases. Given that OKSM (Yamanaka) factors convert somatic cells into induced pluripotent stem (iPS) cells, alterations in transcriptional state could affect destiny of the cells. In this chapter, revisiting known TFs, we would argue if transcription controlling strategies could contribute for the novel therapies on human diseases.

2. Transcription factors (TFs) in mammalian cells

Transcription factors are divided into two groups. First, the general TFs (GTFs), including preinitiation complex components TFIIA, TFIIB, TFIID, TFIIE, TFIIF, and THIIH, are the primary protein factors that are required for the initiation of transcription from the TATA box (or TATA element), then elongation is executed by RNA polymerase II (RNA pol II) [1]. The others are the site-specific TFs or the DNA sequence-specific binding proteins.

2.1 The GTFs and TATA-less promoters

Molecular mechanisms of the initiation of transcription from TATA box have been well known as the most essential nuclear events in mammalian cells. However, about 70% of mammalian gene promoters have no TATA or TATA-like elements, and they are referred to as TATA-less promoters [2]. In yeast cells, most of genes are regulated by the same general TF-dependent system independent of TATA or TATA-like sequences [3]. TATA-containing and TATA-less promoters

are different in the distribution of the A-tracts, G-quadruplex, and CpG islands [4]. Given that most of the housekeeping genes are controlled by TATA or TATA-like elements, TATA-less promoters would be sensitive to the environments in response to various stresses. For example, some of the TATA-less promoters have DTIE binding sites [5]. The duplicated GGAA (TTCC) elements are frequently found near the transcription start sites (TSSs) of the human TATA-less promoters [6], implying that GGAA (TTCC) binding TFs contribute to the initiation of transcription.

2.2 The site-specific transcription factors

Transcription mediator interplays with the transcription activator proteins and the GTFs to enable plasticity and flexibility of gene expression [7]. However, site-specific TF-mediated and TATA-independent transcription system should be investigated because it may control responses to stresses. The TFs are categorized by their amino acid sequences or domain structures according to TRANSFAC (www.edgar-wingender.de/huTF_classification.html) database [8]. Some proteins might have multiple characteristic motifs.

2.2.1 Basic helix-loop-helix (bHLH) proteins

The bHLH proteins contain a basic region and HLH motif, which is comprised of two α-helices separated by a loop [9]. The bHLH family, BMAL, C/EBP, CLOCK, c-MYC, MYOD, NPAS2, and SREBP1/2, regulates development of mesodermal and neural tissues.

2.2.2 Helix-turn-helix (HTH) proteins

The ETS, FOX, IRF, HOX, HSF, POU, and PAX proteins belong to the HTH protein group. The HTH domains are present in NANOG, OCT1, PDN, and FLI1 [10]. ETS family proteins [11–13], which bind to GGAA (TTCC)-core motifs, contain ETS domain [14]. They regulate oncogenesis, development, differentiation, and apoptosis. The homeodomain (HD) is classified into 16 major subclasses, including ANTP, HNF, POU, PRD, SIX/SO, and ZF [15]. The HD proteins, including OTFs [16], which consist about 15–30% of TFs in animals, regulate differentiation and development of organisms.

2.2.3 High-mobility group (HMG) proteins and heteromeric CCAAT-binding factors

This group includes SOX [17] and NF-Y [18] proteins. They are thought to be the key TFs to regulate differentiation of cells, development of organs, and aging.

2.2.4 Immunoglobulin-fold proteins

This group, including NF-κB, IκB, NFAT, STAT, and p53, plays roles in transduction of biologically important signals to nuclei in response to cytokine-induced stimulation, viral infection, DNA-damage, and nutrients.

2.2.5 Leucine zipper proteins (bZIP)

The bZIP family includes CREB/ATF, BACH1/2, and FOS/JUN. The FOS/JUN has been originally characterized as product of the proto-oncogene or immediate

early gene, which very quickly responds to neuronal stimulatory or cellular proliferation-inducing signals [19].

2.2.6 Zinc finger motif containing proteins

The zinc finger motifs, which could be separated into major two classes, (1) Cys_4 and (2) Cys_2His_2, are the major motifs in numbers of TFs and DNA binding proteins [20].

1. The Cys_4-type proteins, including GRs, ERs, RARs, CREBBP, IGHMBP2, GATA, PPAR, are classified into zinc fingers ZZ (ZZZ), zinc fingers AN1 (ZFAND), and GATA zinc-finger domain-containing (GATAD) types.

2. The Cys_2His_2, or the zinc fingers C2H2 (ZNF) type, is the typical motif in the mammalian TFs. SP1, KLF4, KLF5, EGR3, and numbers of ZNF proteins belong to this class.

2.2.7 β-Structure (β-scaffold, β-sheet, and β-barrel) containing transcription factors

This group includes DBP, NF-1, HMGA, SMAD, and TBP. The RNase II and DNA glycosylases carry common motif, TBP-domain. The origin is thought to trace back to before the divergence of the three domains of life, bacteria, archaea, and eukaryote [21].

The classification implies that TATA-dependent initiation is not the standard but one of the site-specific transcriptions. For correct understanding of the cellular responses to differentiation/development-inducing signals, it should be examined how the site-specific TFs could initiate transcription.

3. Stresses and signals that regulate gene expression

Water-insoluble factors, steroids, and vitamins will easily go through lipid bilayer to bind to nuclear receptors. On the other hand, water-soluble compounds bind to the membrane receptors to transfer signals into cells, causing prompt response to induce certain signal cascade [22] to enhance/suppress specific gene expression as follows:

1. cyclic AMP (protein kinase A) pathway

2. MAP kinase pathways

3. Wnt signaling

4. TGFβ signaling

5. JAK/STAT pathway

6. Toll-like receptor signaling

7. immunoreceptor signaling

Cells are continuously receiving stresses, which are, for example, temperature, lights and radiations, proton and ionic gradient, nutrients, and pathogens, including bacteria and viruses. Therefore, responses to these stresses are essential for life [23]. The stress-induced signals will be converted to cellular responses, including secretion, gating ion channels, cellular behavior, proliferation, differentiation, senescence, apoptosis, and the development of organs. Some of the signals cause epigenetic changes or affect transcription of specific genes. We should remember that DNA methylations are required for setting accurate TSSs [24]. The epigenetic modification of DNAs, such as methylation, acetylation, and phosphorylation, and poly(ADP-ribosyl)ation, is dependent on the substrate molecules, S-adenosyl methionine, acetyl-CoA, ATP, and NAD^+, respectively [25]. They are the metabolites that we have learned from textbooks in biological chemistry. These molecules are so essential and indispensable for living things that they must be obtained from metabolism of nucleic acids, amino acids, lipids, and carbohydrates. Not only the epigenetic regulation, but also transcription is dependent on nutrients or the metabolites. For example, AMPK-FOXO pathway plays a role as a nutrient sensor to affect gene expression [26]. The AMPK has been shown to regulate NADPH homeostasis during energy stress [27]. Increased NAD^+/NADH ratio serves as a metabolic switch for transcription of the *BRCA1* gene [28]. The transcriptional corepressor protein, CtBP1, which possesses an NADH binding domain [29, 30], is one of the candidates that play a role in the NAD^+/NADH ratio-dependent transcription system. Importantly, several human DNA-repair-factor encoding gene promoters respond to natural compound *trans*-resveratrol (Rsv), which upregulates NAD^+/NADH ratio in HeLa S3 cells [31], implying that expression of the DNA-repair associated genes is partly regulated by metabolic state.

4. Analyses of gene expression in human diseases

The next-generation sequencing (NGS) analysis greatly contributed for the identification of specific genetic errors [32]. Somatic mutations on cancer driver genes have been identified [33, 34] and the statistical data contribute for the prediction or diagnosis of cancer. In search of biomarkers and cancer-causing factors, transcriptome analyses have been applied on model animals and clinical samples from patients, gradually unveiling mechanisms of the cancer progression. Hot spot somatic mutations are observed in the promoter regions of the human cancer genomes [35]. Binding of the TFs on the promoter could regulate mutation rate to modulate both transcription and DNA-repair systems [36]. In melanomas, such mutations are highly found on the human *TERT* gene promoter [37, 38]. Thus, cancer-causing mutations are not only present in the protein-coding genes, but also in the gene expression regulatory regions.

Transcriptome analysis does not only contribute to the diagnosis or prognosis of cancer but also other human diseases. For example, different gene expression patterns have been shown in autism [39], type 2 diabetes (T2DB) [40], schizophrenia [41], and neurodegenerative disease, including Alzheimer's disease (AD) [42, 43]. Accumulation of repeat containing RNAs in aberrant foci in nucleus has been observed in Huntington disease, muscular dystrophy, and amyotrophic lateral sclerosis (ALS) [44]. The noncoding RNAs (ncRNAs), the long ncRNAs (lncRNAs), or long intergenic ncRNAs (lincRNAs) play essential roles in epigenetic regulation and in conversion of the nuclear structures [45]. Therefore, not only the protein encoding genes but also the ncRNAs are thought to be involved in the pathogenesis [46–48]. The lncRNAs control chromatin structure and nuclear architecture to regulate transcription in eukaryotic cells [49]. Thus, it is very important to explore how the lncRNAs are being regulated. Conversely, introduction of lncRNAs could be applied for treatment of specific diseases.

5. Application of transcriptional control on medical sciences

Varieties of human diseases could be caused by the dysregulation in transcription of either or both protein-encoding genes and ncRNAs. Although, it has not been examined if alteration in transcription is applicable for treatment of the presently intractable diseases, it will be possible in principle. A number of natural and chemical compounds could affect gene expression. Alternatively, transcription could be modulated by the introduction of expression vectors, which express specific TFs in the target cells. In an effort to reach that goal, we have to develop reliable methods to deliver genes into abnormal or lesion cells.

5.1 Natural and the derivative compounds that regulate transcription

Natural compounds or phytochemicals could be applied on treatment of specific diseases. Some of them affect the JAK/STAT signaling pathway that activates cell cycle/proliferation-controlling factor-encoding gene expression [50]. Sulforaphane targets Nrf2 [51], which responds to oxidative stress, implying that it can be applied for the treatment of metabolic syndromes [52]. Tannic acid, coumarins, and chalcones suppress 12-*O*-tetra decanoylphorbol-13-acetate (TPA)-induced HIV promoter activity in human Jurkat cells [53]. Rsv induces promoter activities of DNA-repair factor-encoding genes, including *TP53*, *WRN*, *TERT*, and *HELB* [54–56]. The GGAA-containing motif and the GC-box have been suggested to play an essential role in the response. Vitamin E and the related compounds, including tocotrienols, activate transcription by binding to estrogen receptors [57] but inactivate NF-κB activity [58]. Curcumin, which is a diferuloylmethane from the Indian spice turmeric, also targets NF-κB and AP1 to affect survival and proliferation of cells [59], might be applied on the suppression of the *APP* and the beta-site APP cleaving enzyme 1-encoding *BACE1* gene expression [60].

These observations imply that phytochemicals could be used for therapeutic use. To minimize side effects, how the molecular mechanisms affect transcription should be elucidated. Next-generation therapies for intractable human diseases might be enabled by introduction of TF-expression vectors or by editing specific site(s) of the genome. Additionally, nucleotides or nucleic acid-based pharmaceutical compounds might be developed to ameliorate profile or status of gene expression in dysregulated cells.

5.2 Dysregulation in transcription might cause aging-related diseases

Indeed, aging is not a disease in principle. However, incidences of specific diseases are increased according to the process, for example, arteriosclerosis, cancer, sarcopenia, and neurodegenerative diseases, including AD. The causations of aging have been studied and discussed at the cellular level and they could be classified as follows:

5.2.1 Genome instability, including telomere shortening

Aging is thought to be accelerated by the accumulation of damage on chromosomal DNAs. This hypothesis is supported by the identification of responsive genes for premature aging, for example, LMNA, WRN, ATM, and SRPTN [61, 62]. Therefore, the aberrances in the nuclear architecture and DNA repair systems may cause premature aging. Cellular senescence is generally accompanied with the shortening of telomeres [63]. This is consistent with the observations that shortened telomeres cause genomic instabilities.

5.2.2 Accumulation of damage from oxidative stresses

Neurotoxicity could be induced by numbers of factors. The oxidative stress or the oxidative damage would cause neurodegenerative diseases, including the AD. The oxidative stresses impact on the Keap1-NRF2-ARE signaling pathway to upregulate expression of stress response genes, such as *NRF2*, *KEAP1*, *SOD1*, and *ETS1* [64]. The observation is consistent with the theory that the incidence of the AD increases with the aging [65].

5.2.3 Mitochondrial dysregulations and dysfunctions

Morphology of mitochondria and the respiratory functions are declined by aging process, accompanied with the accumulation of mitochondrial DNAs (mtDNAs) [66, 67]. The mutations on the mtDNAs are thought to be partly caused by the oxidative stresses. Nuclear-mitochondrial communication is thought to play a role in the regulation of longevity [68]. Moreover, telomere dysfunctions induce mitochondrial compromise [69]. In summary, interplay between mitochondria and nuclei would affect aging.

5.2.4 Decrease in the cellular NAD^+ level

Nicotine amide adenine dinucleotide (NAD^+), which is required for the respiratory functions of mitochondria, regulating enzymes in TCA cycle, and oxidative phosphorylation (OXPHOS), is declined with aging [70, 71]. The NAD^+ activates protein deacetylase Sirtuins, which regulate health span and life span. Moreover, the NAD^+ is a substrate for poly(ADP-ribose) (PARP), which plays an essential role in the DNA damage response [31].

5.2.5 Alteration in the epigenetic regulations of the genomes

The profiles of the methylation of DNAs and the modifications, including acetylation and methylation of histones, are altered in the aging process [72, 73]. These epigenetic changes will enhance or reduce transcription of specific genes.

5.2.6 Alterations in immune response and cytokine dysregulation

Cytokine dysregulation or prolonged inflammation is observed in aged person [74]. Numbers of proteins are involved in the inflammation process, suggesting that expression and degradation of proteins could accelerate or decelerate cellular senescence.

Aging might start from subtle changes in the TFs profile that regulate expression of genes encoding DNA-repair/mitochondrial/immune response-associated protein factors [31, 75]. Decline in metabolites, which target DNA-binding proteins and ncRNAs [46–48] to modulate epigenetic systems [24–30], would accelerate aging. Given that alterations in the transcription could cause the aging, it could be slowed by manipulating TFs profile.

6. Concluding remarks and future prospects

Homeostasis or negative feedback is not only required for endocrine system but also for biochemical reactions. Metabolites, including sugars, lipids and amino acids, and ionic substrates need to be maintained within biologically significant

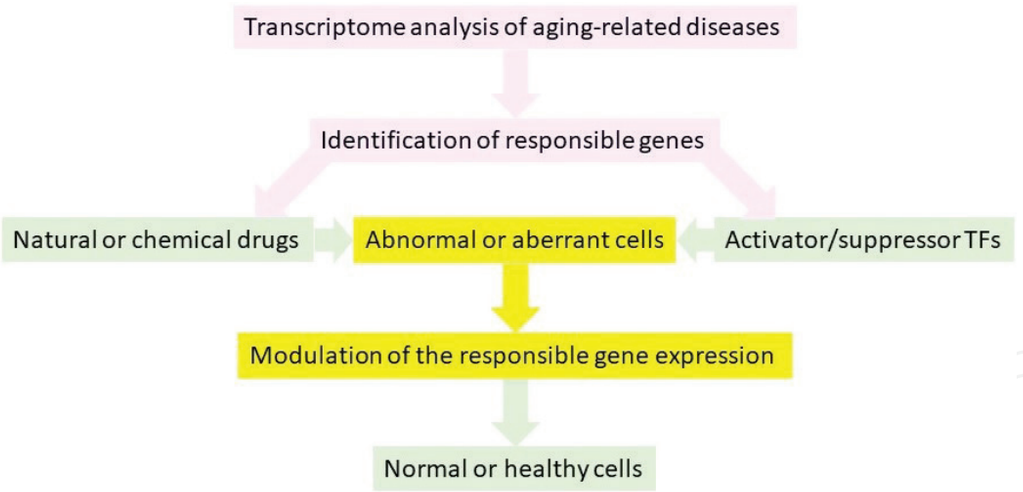

Figure 1.
Concept of the next-generation transcriptome-based therapeutics.

level. Similarly, nucleic acids and proteins should be appropriately managed being continuously synthesized and degraded. The equilibrium will gradually change in accordance with aging. Homeostasis in organs would play a role in the cancer generation [76]. Senescence can be metaphorically expressed as a walk on a balance beam that is narrowed afterward. The younger cells proliferate faster and respond to stresses with more accuracy than the older ones. After repeated proliferation, cells will reach the point where they cannot go forward but initiate aging. Somatic cells can acquire a pluripotency by incorporation of TFs. So, is it not possible to reverse aged or abnormal cells into younger or healthy cells? Then, what molecules (nucleic acids, proteins, etc.) are required and how they are introduced (by specific vectors, genome-editing systems, etc.) into cells? That should be answered for the next-generation therapeutics against aging-related diseases (**Figure 1**).

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Conflict of interest

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.

Abbreviations

ALS	amyotrophic lateral sclerosis
AD	Alzheimer's disease
GTF	general transcription factor
HD	homeodomain
NAD^+	nicotine amide adenine dinucleotide
bHLH	helix-loop-helix

HTH	helix-turn-helix
lncRNA	long noncoding RNA
mtDNA	mitochondrial DNA
ncRNA	noncoding RNA
TF	transcription factor
TSS	transcription start site

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