Alteration in Transcriptional State, as a First Step in Cancer Development

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Abstract

The risk of cancer, which increases in accordance with aging, has been mainly explained by the oxidative stresses that cause DNA damage. In fact, recent DNA sequencing studies of genomes from cancer patients revealed a variety of mutations on specific genes, suggesting that accumulation of DNA damage is the main cause for development of cancer. Therefore, great effort has been undertaken to analyze DNA mutations. On the other hand, especially for clinical diagnosis, abnormalities in metabolism, including up-regulation of glycolysis or "Warburg effect", are known to be characteristics of cancer. Taken together, cancer could be referred to as both "genetic disease" and a "metabolic disease". We have confirmed that numbers of DNA-repair- and mitochondrial function-associated gene promoters commonly contain a duplicated GGAA-motif, which is a target for multiple transcription factors. In this article, we will tentatively draw a hypothetical mechanism behind the generation of cancerous cells, in which alterations in transcriptional state have occurred primarily with repeated divisions or aging of normal cells. Thus, cancer could be regarded as a "transcriptional disease". We hope this concept contribute for innovation of a new cancer therapeutics targeting transcription.

Keywords: Cancer; DNA repair; Mitochondria; Metabolism; Senescence

Editorial

It has long been argued how and why cancers are generated. In general, it is believed that cancer is a genetic disease that is resulted from mutations on driver genes, including PIK3CA, IDH1 and RB1 [1]. Moreover, next-generation sequencing enabled diagnosis of cancer and diseases that are thought to be occurred from genomic alterations [2]. Another aspect of cancer is that it is a metabolic disease [3]. It is widely known that cancer consumes more glucose to produce ATP by glycolysis or fermentation. The metabolic state of tumor cells has been referred to as the "Warburg effect" [4]. Importantly, TCA-cycle enzymes, FH (Fumarate hydratase) and SDH (Succinate Dehydrogenase) have been suggested as tumor suppressors [5]. Deficiency in oxidative phosphorylation (OxPHOS), which is dependent on an adequate supply of NADH and FADH2 from TCA cycle, has been suggested to play a causative role in cancer development [6,7]. We have confirmed that a cis-element, namely duplicated GGAA motif, is present near transcription start sites of the CS, ACO2, IDH1, IDH3A, IDH3B, SUCLG1, SDHAF2, SDHB, SDHC, FH, and ACY1 genes, which encode enzymes in the TCA-cycle [8]. Moreover, the motif is contained in the bidirectional promoter regions of the genes encoding components of the OxPHOS complex, such as NDUFA1, NDUFA2, NDUFB3, NDUFB9, NDUFC1, NDUFS1, and NDUFS3 [8].

It is well established that epigenetic and/or transcriptional change play a role to determine chromatin states in tumor cells [9]. Recent genomic studies indicated alterations in gene expression in many human diseases [10,11]. Whole transcriptome analysis indicating cis-quantitative trait loci (QTLs) has been reported as of value for revealing gene expression and transcription state in cells from patients of specific disease [12]. Cancer incidence in humans increase exponentially with age, suggesting that aging is the strongest demographic risk factor for most human malignancies [13,14]. These events could be explained by reactive oxygen species (ROS) generation and accumulation of DNA damage on chromosomes or increased genomic stability, including telomere shortening [14]. Moreover, hypoxia, which attenuates response to DNA damage, increase mutation rate and chromosomal instability, may play a part in linking cancer with aging [15,16]. Importantly, aging is accompanied with epigenetic change and alteration of gene expression profile [17,18]. Numbers of GGAA motif-binding transcription factors (TFs), which act as positive and negative transcriptional regulators, may drive mitochondrial- and DNA repair-factor encoding genes simultaneously. However, repeated cell division and extracellular signals will gradually disturb the profile of TFs that bind to the GGAA (TTCC) motifs, and finally lead to disruptions in mitochondrial functions and DNA-repair systems. At this stage, cells will exhibit abnormalities in metabolism carrying mutations on DNAs. These features could be referred to as characteristics of cancer and malignant tumors. Moreover, DNA damage will activate poly(ADP-ribose)ylation resulting in over consumption of NAD+ molecules that are required for synthesis of poly (ADP-ribose). The reduction in NAD+/NADH ratio will disturb the progression of the TCA cycle until it does not function for sufficient ATP production. In this way, cells can no longer depend on the normal respiration system, but must up-regulate glycolysis and fermentation (Figure 1).

Thus it might be too late to treat cancer after identification of mutations on driver genes, because they have already abnormalities in DNA repair and mitochondria, which frequently cause chemoresistance. Moreover, most of the anti-cancer drugs have been developed under the concept to kill cancerous cells, but sometimes they have heavy side effects on patients. A novel concept is required to treat pre-malignant cells to be converted into benign state.

It remains unclear how the GGAA motif has been duplicated and incorporated into regulatory regions of various genes encoding DNA repair- and mitochondrial-factors. However, the duplication of TF
binding site might have been advantageous for organisms in the course of evolution.

The crystal structure of mouse Elf3 with type II TGF-β receptor promoter was reported [19], representing an association model of the ets motif binding protein with the duplicated GGAA motifs. The sequence is recognized by at least twenty seven ETS family proteins and other TFs, including GABP, NF-kB/c-Rel, and STAT proteins. Therefore, transcriptional efficiency could be fine-tuned with the distance between GGAA (TTCC) sequences, variation of the flanking sequences and the combination of the binding factors.

Figure 1: Dysfunction of tricarboxylic acid (TCA) cycle, which could be caused by attenuation of GGAA-dependent transcription. Duplicated GGAA-motifs are contained in the 5'-upstream regions of the ACO2, GLUD2, IDH1, IDH3A, IDH3B, MDH2, ME2, SUCLG1, SDHA/F2/SDHB/SDHD, FH, ACLY, CS, and PDHX genes. Various cellular stresses, including chemicals, X-ray and UV irradiation, virus infection, and aging, may alter the transcriptional state leading to disruption of the mitochondrial function- and DNA repair-associated gene expression. Damage on DNAs activate PARP enzyme, which consumes NAD+ molecule to synthesize poly(ADP-ribose), may further lead to dysfunction of the TCA-cycle. Thus cells must depend on glycolysis to synthesize ATP. The consequence could be referred to as the "Warburg effect". This hypothesis implies that pre-cancerous state could be prevented if NAD+/NADH ratio were ameliorated.

Here we propose a mechanism in which alterations in the transcriptional state of cells leads to insufficient mitochondrial function and DNA repair system. Given that introduction of OSKM transcription factors reprogram cells to gain pluripotent ability [20], enforced expression of specific TFs may improve metabolism in cancerous cells. In order to access this possibility, elucidation of how specific causal regulatory effects by integration of expression QTLs with complex trait genetic associations. PLoS Genet 6.

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