HIGH SCHOOL EDITION
Journal of Student Research
Volume 10 Issue 1 (2021)

Transcription and Cancer in Eukaryotes

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ABSTRACT

Organisms demand pinpoint and correlated gene expression controls for growth, advancement, and operation. This control is also known as transcriptional regulation. It is a complicated process especially in eukaryotes since it is responsible for all biological processes, any chemical reactions within an organism. Transcription control and its concept were brought up about half a century ago[1]. These concepts gave a basic understanding on DNA binding transcription factors (*trans*-factors) which inhabit specific DNA sequences at control elements (*cis*-elements). They regulate transcription apparatus[2]. Mis-regulation of transcription may cause failure of gene expression that is responsible for cell division, through disproportionate activation of once positively acting transcriptional factors and nuclear oncogenes[3]. Epigenetics is learning heritable alterations in gene expression that do not occur and involve in DNA sequence. These changes can be established all the time almost randomly, and alternations are passed and inherited through cell division and replication, allowing cells to have different identities while having the same genetic sequence. Due to loss of epigenetic control and failure of keeping proper epigenetic marks, which result in inappropriate activation and will lead to disease state including cancer[4]. This review focuses on transcriptions, epigenetics, cancers, and potential therapies to regulate and control cancer cells.

Transcriptional Regulation

In the nucleus of a eukaryote, the genetic material is tightly packaged in an orderly manner into many linear chromosomes5. Transcription is far more complex in eukaryotes. It requires RNA polymerase II, general transcription factors (GTFs) and proteins (transcriptional factors) (Fig. 1) to work together to capture short DNA sequences (cis-acting elements) in the non-coding region of gene3.

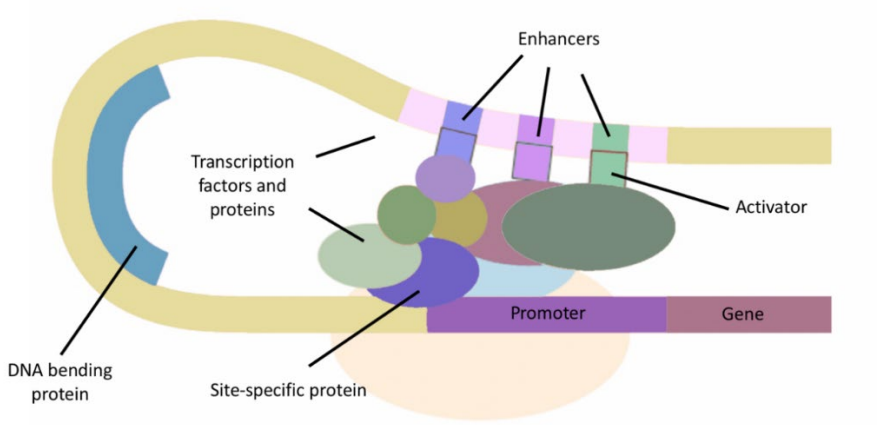

Fig. 1. Transcription factor interact with all types of protein to promote transcription.

Transcription of genes will result in an increase of protein levels. RNA polymerase binds and converts DNA to mRNA. It forms a complex with basal transcriptional factors. mRNA travels to the ribosome for translation and is then converted to amino acids sequence and protein folding[5].

Eukaryotes require multiple proteins to work together to express a gene. The whole process will allow genes to be turned on and off accordingly. Transcription factors regulate gene expression through enhancers, repressors, cofactors, and RNA polymerase II[2]. Transcriptional factors control initiation and elongation, which are the functions of activators and repressors. Transcription factors regulate gene expression by binding to enhancers and coactivators, which lead to the binding of RNA polymerase II and in turn binds to GTFs (activator protein). An enhancer is a region of DNA that can be bound to transcriptional factors or proteins that increases the chance of transcribing a particular gene. Repressors are the opposites. They bind to the operator region of the promoter, preventing binding of RNA polymerase, which decreases the chance of transcribing the gene. Cofactors stabilize the DNA loop between the enhancer and the start site, including mediator complex and cohesin[2]. RNA polymerase II starts transcription from the start site or the initiation site, working its way downstream. It goes from 3' and creates a strand that goes from 5' to 3'. This process is also known as elongation. Various transcription factors and cofactors recruit elongation factors which then phosphorylates the polymerases and pause release factors, allowing elongation to proceed[2]. Transcription is affected by various kinds of protein during the whole process, since they modify and bind to histone in nucleosomes. Different cells also transcribe different sets of genes.

Epigenetic Control

Epigenetics is a term to describe inherited modifications that are not present in DNA sequence and cells still contain the same genetic information. Epigenetic controls regulate gene expressions in various levels. These include DNA methylation and histone modifications. Epigenetic mechanisms can also regulate miRNA, which would be discussed later in the paper. DNA methylation is a process where methyl groups are added to DNA molecules. It typically acts to repress gene transcription. It is a secure way of silencing genes that is crucial to regulate gene expression and chromatin architecture[6]. It commonly occurred by the covalent modification of cytosine residues in CpG dinucleotides[4]. CpG dinucleotides concentrated in a short DNA stretch called "CpG islands". CpG islands remain unmethylated while most of the other sites are. However, some CpG islands promoters might be methylated during growth, and thus might result in long-term transcriptional silencing[4]. Interestingly, this process can result in X-chromosome inactivation. DNA methylation affects the growth of various somatic tissues, acting primarily on developmentally important genes[7].

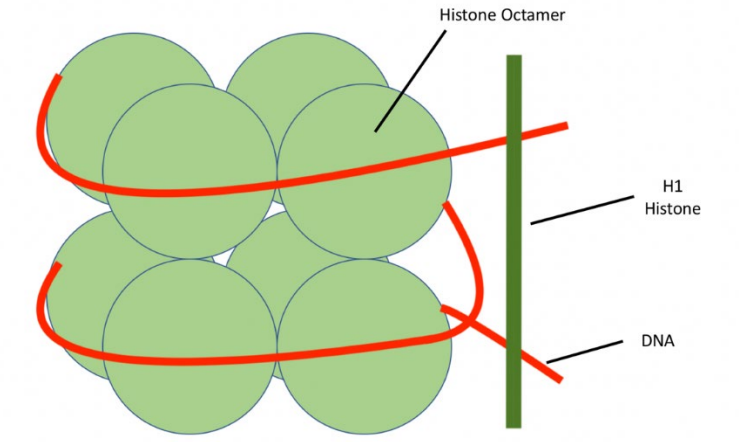

Fig 2. A nucleosome where DNA wraps around histone octamer, an eight protein complex consists of 2 copies of four core histone proteins (H2A, H2B, H3 and H4). They all provide structural support to a chromosome and can regulate gene expression.

DNA has a double helix structure and is packaged tightly within a cell's nucleus. It is wound around proteins called histones (Fig 2). Histone packages DNA into nucleosomes and is also the main protein in chromatin. It condenses long DNA molecules into more compact structures[8]. DNA wraps around histone to regulate its gene. A histone consists of a C-terminal domain and a N-terminal tail, and the N-terminal tails of histones are capable of going through various modifications. This protein varies in many forms. Adding modifications like writers, or deleting modifications like erasers. In addition, some might bind to these modifications like readers including acetylation, methylation, phosphorylation, sumoylation, and more[2]. Acetylation of histones increases the expression of genes through activation, and histone methylation can increase or inhibit gene expression through transferring methyl groups to making histone. Additionally, phosphorylation is a pervasive mechanism of regulating protein and transmitting signals through cells, and sumoylation is a type of cellular process that modifies post-translational protein. Covalent histone modification works by altering chromatin's structure or by recruiting histone modifier proteins and thus changes many cellular processes[4]. Unlike DNA methylation, histone modification can lead to activation or repression depending on the various types of modification.

Non-coding RNA, especially microRNA, regulates gene expression through post transcriptional silencing of target genes which control a wide range of biological and genetical processes. miRNA is expressed in a target-specific way. Epigenetic mechanisms can regulate the expression of miRNA.

Transcription and Cancer

Cancer is a disease state caused by uncontrollable cell growth and then spread into surrounding tissues[9]. Mutations in certain genes lead to deregulation of cell cycle, cell growth and apoptosis, a form of cell death. This includes mutations involving oncogenes, which promote cell survival. Mutations can also occur in tumor suppressor genes, which normally suppress uncontrolled growth. These types of mutations are well known to be responsible for cancer initiation, promotion and progression. (10) Cancer cells modify their cell-cycle control, and cells won't be able to control their growth.

Myc is a common amplified oncogene, and the expression of this gene is closely related to tumor enlargement. Transcription factor c-Myc plays an important role in tumor cells' development and growth[11]. When high levels of c-Myc is present in tumor cells, transcription factor recruits transcription elongation factor P-TEFb, causing transcriptional amplification[2]. Instead of inhibiting and regulating the set of genes or moving on to a new set of genes when overexpressed, c-Myc amplifies the existing gene expression. Thus, transcriptional amplification allows tumor cells to grow and proliferate by reducing rate-limiting constraints in cells.

In addition to amplification, there are three other main groups of transcription factors that also contribute to cancer: steroid receptors. This includes estrogen receptors, resident nuclear proteins, androgen receptors, and latent cytoplasmic factors, triggered by receptor-ligand interaction at the cell surface[12]. Overproducing or overusing one or more of these transcription factors can lead to unrestrained growth of all human cancers.

Epimutations can lead to aberrant epigenetic control which play a profound role in cancer. They can lead to silencing of tumor suppressor genes and other subsequent effects including genetic mutations or deletions[4]. This can happen in both DNA methylation and histone modification. Apart from that, epimutations can also promote growth of cancer by activating oncogenes. These epigenetic alterations would favor the growth of tumor cells, resulting in their uncontrollable growth. This goes the same with silencers. A silencer is usually referred to as a short, specified sequence of nucleotides located in the 5' upstream promoter region, capable of recruiting transcription factors and carrying out specific genes[13]. Any changes to the silencer would also result in tumor growth, by silencing tumor suppressor genes.

As said, miRNA regulates gene expression, cell proliferation and apoptosis, which are also ways to deregulate tumor growth in cancer. Any changes or mutations in miRNA expression can promote tumorigenesis. At the same time, miRNAs can be suppressing tumor development or acting as oncogenes depending upon their target genes[10].

Breast cancer, for example, is one of the most prevalent cancers across the globe. With symptoms of changing size, shape, and appearance of the breast, it is the most common cancer diagnosed in women in the United States, after skin cancer. The factual cause of this cancer has not been fully discovered, however, just like all other types of cancer, it occurs when some breast cells start to grow abnormally without regulation. Thus, scientists are developing and have come up with a few ways of limiting cell growth by targeting estrogen receptors, which will be discussed in latter sections. In addition, prostate cancer is another common chronic cancer in the prostate gland, used to nourish and transport sperm cells in males. Although it comes with some apparent symptoms, including pain and blood, prostate cancer can be very difficult to cure in late stages. The accumulating cancer cells form a tumor that eventually invades nearby healthy organs. Similar to breast cancer, scientists have approached its therapy by targeting both estrogen receptors and androgen receptors to inhibit uncontrollable cell growth.

Therapies and Future Prospects

Due to the unique characteristics of cancer cells, it is possible to target them specifically and minimize disruption to normal cells. Current cancer treatments involve using chemicals, or drugs, to disrupt cancer cell growth and proliferation. Utilizing the increasing knowledge on transcriptional regulation and gene expression, scientists have developed medicine to target involved transcription factors and epigenetic control in cancer cells.

There are already many ways of targeting transcription factors as therapies for cancer being used, including using small, specific molecules that bind to nuclear hormone receptors (Fig 3). Examples include drugs that regulate the activity of estrogen receptor, androgen receptor, RAR and glucocorticoid receptor, which are currently used to cure cancers, including breast cancer, prostate cancer, leukemia and more[14].

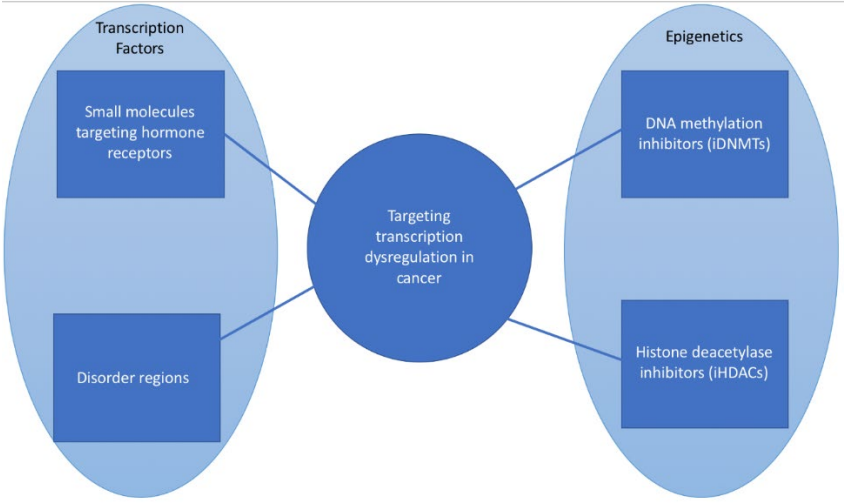

Fig. 3. Current therapies of targeting and using transcription protein to cure cancer. Small molecules targeting hormone receptors and targeting disorder regions fall in with transcription factors, and using various kinds of inhibitors have also been explored to regulation epigenetics.

Approximately 70% of breast cancers previously mentioned rely on estrogen receptor (ER)for sustained cell growth, and a group of breast cancer utilizes ER to sustain their aberrant capabilities[15]. ERs can occur within the cell nucleus, which can function as transcription factors to regulate the production of proteins.as transcription factors to regulate the production of proteins. Eliminating genetic ER in mice increases survival, however animals display abnormalities in the development of some organs[16]. Nonetheless, there are still ways and strategies to target the ER LBD (ligand-binding domains) to suppress cell proliferation and cure cancer. Particular estrogen receptor modulators, including tamoxifen and raloxifene, directly compete with estrogen for binding to the ER LBD[1]. Another way to inhibit

ER is to reduce the amount of estrogen by inhibiting the enzyme that converts androgens to estrogens, aromatase[18]. Preventing activation of estrogen receptors will stop its function as transcription factors. Thus, it won't be able to regulate or limit the production of tumor suppressor genes.

Similar to breast cancers require ER to inhibit the production of tumor suppressor genes, prostate cancers demand androgen receptors (AR) for maintenance and progression[15]. Androgens are hormones like testosterone that promote the growth of normal prostate epithelium, a place in male reproductive system that originates prostate cancer cells. Because of this, recent findings suggest using androgen synthesis inhibitors or inhibitors of ligand-binding to prevent the growth and survival of prostate cancer cells[15].

However, there is more to explore. Approaches like targeting of intrinsically disordered regions of transcription factors (Fig 3) or targeting the auto-inhibited state, could both result in effective ways of curing cancer, but neither one has really been studied[14]. Intrinsically disordered regions are referred to places that do not form a stable structure, which transcription factors frequently contain[19]. Studies showed about 79% of cancer-associated proteins contain an intrinsically disordered region of 30 amino acids or more[20]. These unstable regions can be structured with binding partners, a process called coupled folding and binding[21]. The conventional method tends to preclude such regions as targets due to their lack of structure and the accompanying lack of binding pockets for small molecules to interact[14]. Nonetheless, new approaches suggest the structures of intrinsically disordered proteins actually have a higher proportion of potential cavities where a small molecule could bind than their folded counterparts[22]. This is only a start to cure cancer by targeting intrinsically disordered regions of transcription factors, so there are definitely a lot more to find.

In addition to directly targeting transcription factors, epigenetic approaches in cancer treatment are also utilized. The goal of these epigenetic approaches is to reset the cancer epigenome back to a normal state from multiple alterations. There are two types of epigenetic drugs that have been approved by the US Food and Drug Administration for now: DNA methylation inhibitors (iDNMTs) and histone deacetylase inhibitors (iHDACs) (Fig 3)[23]. iDNMTs for example, by inhibiting DNA methylation transferases (DNMTs) in replicating cells, causes the loss of methylation marks during cell division and DNA replication. In another word, the reactivation of aberrantly silenced tumor suppressor genes by iDNMTs would restore their expression and function[23].

Conclusion

A considerable amount of work has gone into understanding eukaryotic transcription and epigenetics. The mechanisms of gene expression, including the steps of transcription, enhancers, promoters, and repressors, are well understood. DNA methylation and histone modification are two main ways of epigenetic control. Loss of transcriptional control can lead to cancer in eukaryotes. Many cancers and tumor growth relate to silencing transcription factors such as Myc. The silencing of tumor suppressor genes within epigenetic control can also lead to cancer. miRNAs that limit cell proliferation and gene expression have been used to cure tumor cells with uncontrollable growth. In addition, several therapies including binding nuclear hormone receptors are used to cure breast cancer.

While we have already started to develop cancer treatments by targeting transcription, there is far more to expect and to learn from these topics: new transcription factors to be discovered, new ways to decipher epigenetic code, and new therapies for cancer treatment. It is clear that we just started exploring transcription and cancer, and our understanding is superficial at this time.

Acknowledgments

I would like to thank and give my appreciation to everyone who helped with this review. Especially, the appreciation goes to Mr. Tyler David Perdue and Mr. Kevin Quick as my mentor for this paper who are always encouraging through the entire process during this difficult time.

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