Gene expression regulation and cancer

M. Dolores Delgado and Javier León

Grupo de Biología Molecular del Cáncer. Departamento de Biología Molecular. Unidad de Biomedicina-CSIC. Universidad de Cantabria. Santander. Spain.

Gene expression is mostly controlled at the level of the transcription initiation. The transcription control regions of protein-encoding genes include: the core promoter, where RNA polymerase II binds, the proximal and distal promoter, responsible for gene expression regulation, and the enhancers and silencers. Chromatin represents an additional level of regulation of gene expression. The switching between inactive and active chromatin is closely related to the activity of histone-modifying enzymes and chromatin-remodelling complexes. Transcriptional activation of a gene requires the binding of specific transcription factors to regulatory DNA elements, the opening of the chromatin, the binding of Mediator, and the assembly of the preinitiation complex with RNA polymerase and RNA synthesis initiation. Transcription factors ultimately transduce the proliferation signals elicited by growth factors. Moreover, many human oncogenes encode for transcription factors, and some of them are prevalent in particular neoplasias (e.g., MYC, MLL, PML-RARα). Also, some of the most prominent tumor suppressors (e.g. p53) are transcription factors.

Key words: transcriptional regulation, promoter, enhancer, chromatin modifications, oncogenic transcription factors, RNA polymerase II.

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Correspondence: J. León.
Departamento de Biología Molecular.
Facultad de Medicina.
Universidad de Cantabria.
39011 Santander. Spain.
E-mail: leonj@unican.es

INTRODUCTION

Gene expression can be regulated both at the transcriptional and post-transcriptional levels. Post-transcriptional mechanisms include the stability of mRNAs, the intracellular location of mRNAs, the rate of mRNA translation in polysomes and the protein degradation rate (probably the most important post-transcriptional regulatory mechanism). However, the prevalent regulatory point of gene expression is the transcription rate. Transcriptional activity is the responsible for the steady state levels of mRNA of the regulated gene, which in turn correlates with protein levels for most genes. In this review we will focus on the transcriptional control of gene expression. We will first review the regulatory sequences and chromatin modifications involved in transcriptional control and then the proteins that, by binding these sequences, trigger the transcription of the gene. Finally, a number of important oncoproteins and tumor suppressor proteins are transcriptional regulators, and some of the most prevalent in human cancer will be briefly reviewed.

REGULATORY SEQUENCES IN THE MAMMALIAN GENE

Anatomy of the structural genes

Transcription of eukaryotic genes requires three different RNA polymerases. RNA polymerase I transcribes the ribosomal genes. RNA polymerase III transcribes genes for small RNAs, including those for tRNAs. All the protein-encoding mammalian genes, as well as microRNA genes, are transcribed by the RNA polymerase II (RNAPII hereafter), which actually is a multi-protein complex known as RNAPII holoenzyme[1]. These genes are often referred to as class II genes. The rate of transcription is mostly controlled at the level of the transcription initiation by RNAPII, which in turn depends on the rate of RNAPII binding to the initiation site and the activation of its RNA polymerase activity. Although there is a great variability in gene structure, the figure 1A represents a

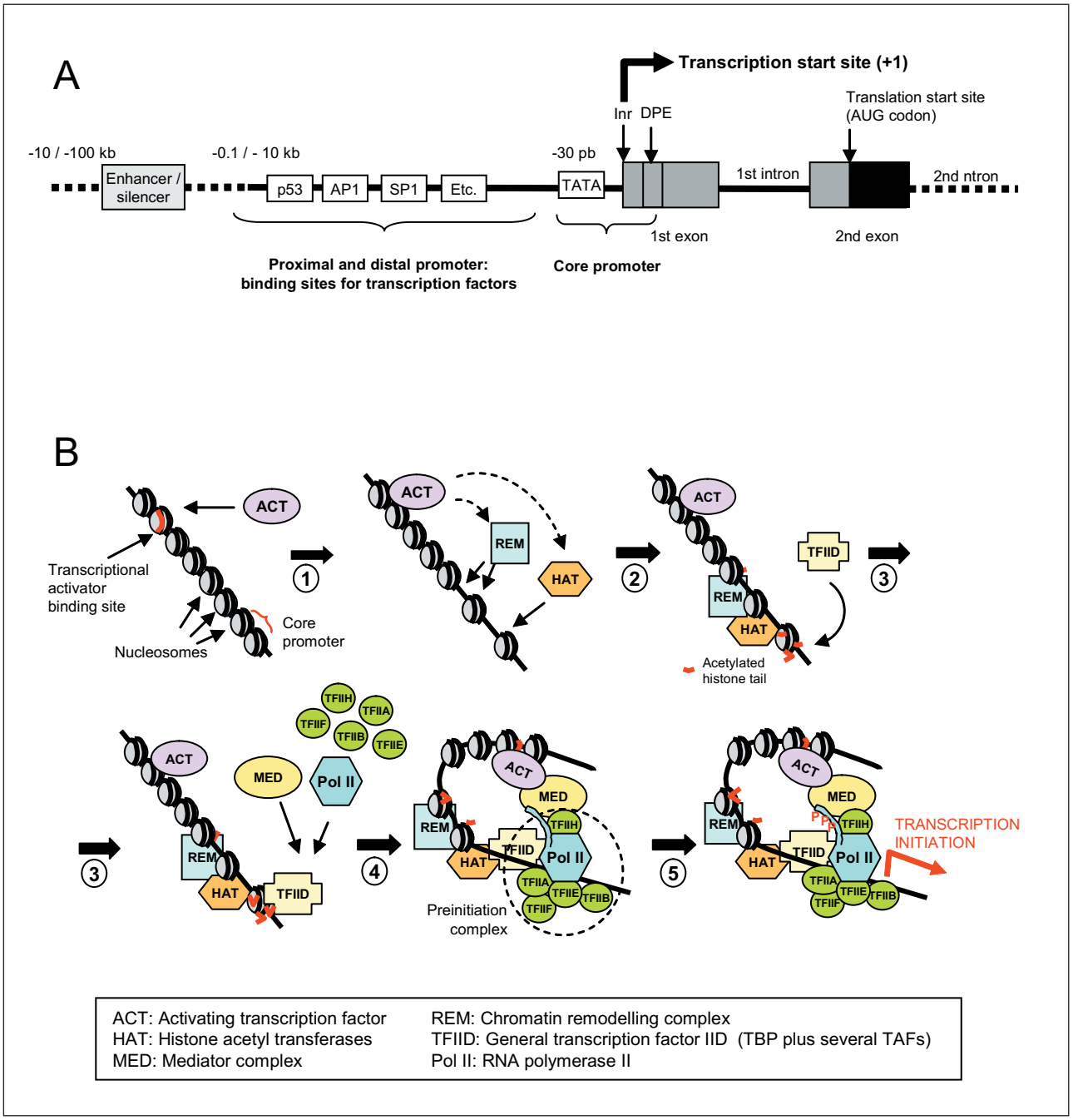

Fig. 1. A) Scheme of the 5' regulatory regions of a typical gene transcribed by RNAPII. The core promoter (with the TATA box, Inr and DPE box, described in the text), the proximal and distal promoter (with the binding sites for transcription factors) and the enhancers and silencers. Depending on the particular gene, the enhancer can be located downstream of the gene and the translation start codon on the first or second exon. B) Scheme of the activation of the transcription of a gene. The process is initiated by the binding of the activator to its regulatory target sequence (1). The activator recruits chromatin remodelling and histone acetyl transferase complexes (2), which open the chromatin into an accessible conformation for the TFIID complex (3) (composed by TATA-binding protein and TAFs). Next, Mediator complex is recruited to bridge the activator and the RNA polymerase II (Pol II), to form the preinitiation complex (4). Once this complex is assembled, the CTD domain of the RNA polymerase is heavily phosphorylated and the RNA polymerization starts (5). The different protein complexes are not drawn to scale.

scheme of a «typical» class II gene. The gene sequences are numbered given the +1 coordinate to the first nucleotide transcribed into the mRNA, i.e. the transcription start site.

The transcription control regions of eukaryotic class II genes can roughly be classified into three categories: *a)* The core promoter, where RNAPII will bind, *b)* the proximal and distal promoter, i.e., the set

of sequences responsible gene expression regulation, and *c)* the enhancers and silencers, sequences that exert activating and repressing gene expression activity, respectively, and are located at larger distances from the transcription start site[2].

The core promoter

The core promoter comprises the transcription start site and flanking sequences extending about 50 bp in each direction. The core promoter is the region where the RNAPII holoenzime will bind to assembly the transcription pre-initiation complex and initiate transcription. The TATA box, the initiator element (Inr) and the downstream promoter element (DPE) are generally known as core promoter elements of class II genes[3,4]. The TATA box has a consensus TATA(A/T)A(A/T) sequence and is usually located ~ 25-35 bp upstream of the transcription start site, +1. The Inr, which has a consensus PyPyAN(T/A)PyPy sequence (Py, pyrimidine; N, any nucleotide), is located around position +1 and the DPE, with consensus sequence PuG(A/T)CGTG (Pu, purine), is centred around position +30. However, most genes do not contain the three elements. Thus, the DPE is most commonly found in TATA-less promoters, although some promoters contain both DPE and TATA motifs[5]. In TATA-less promoters, the transcription begins at any one of multiple possible sites over an extended region, often 20-200 base pairs in length. As a result, such genes give rise to mRNAs with multiple alternative 5' ends. These genes generally are transcribed at low rates, whereas genes carrying TATA box in their promoter are usually transcribed at higher levels and show a more accurate transcription initiation than TATA-less genes[5].

Regulatory sequences in the proximal and distal promoter

Whereas the core promoter is defined by the binding of RNAPII complex, the rest of the promoter is the set of DNA elements, i.e., DNA sequences recognized by specific transcription factors[2]. These regulatory elements are short (typically 6-10 bp) and, although they are identified by a consensus sequence, they can vary in their exact sequences. Thus, any particular element may appear thousands of times over the genome. The boundaries between «proximal» and «distal» promoter are diffuse. The term proximal promoter is commonly used to design a set of regulatory DNA elements lying within 100-200 base pairs upstream of the start site, although it is also frequent to find them in the first exon and intron. Proximal promoter includes elements which are present in many promoters. They set the basal level of transcription initiation, without responding to any tissue-specific or developmental signals. These include: the CAAT box, recognized by the activators NF-1 and NF-Y, the octamer module, recognized by Oct-1 and the GC box, recognized by the Sp1 activator. TATA-less promoters generally initiate transcription with RNAPII at Inr sequences associated with Sp1 binding. Distal promoter elements can map as far as 10 kb upstream from the transcription start site. Many of these elements confer tissue-specific expression. The minimal upstream sequences capable to direct expression of a gene is usually referred to as minimal promoter, and usually comprises the core and the proximal promoter. Actually, the promoters of many tissue-specific genes are a highly valuable research tool as these sequences can direct tissue specific expression of any given gene engineered downstream of the promoter.

Enhancers and silencers

Enhancers are defined as cis-acting DNA regulatory elements that stimulate transcription, independently of their position and orientation with respect to the transcriptional initiation site[6-8]. Silencers have the opposite effect: silencers are cis-acting sequences that are bound by repressors, thereby inhibiting activators and reducing transcription. Enhancers and silencers are similar to promoter regions in that they are organized as a series of sequences that are bound by regulatory proteins. Typical mammalian enhancers span 200-1,000 bp, and can bind to dozens of sequence-specific proteins[2]. However, they are distinguished from promoter elements by being able to act at a distance (sometimes 50 kb or more), and by being active regardless of their location with respect the gene they control. Thus, enhancers can be found upstream, in an intron or even downstream the gene. Enhancers have been identified for many genes of the mammalian genome, whereas silencers are less frequent. Like promoter-proximal elements, many enhancers are cell-type specific. Genes expressed in an ordered pattern during development or differentiation are regulated by complex transcriptional enhancers called locus control regions (LCRs)[7,8].

Insulators

Insulators are DNA sequences that can establish boundaries of fixed location. Insulator elements found from yeast to man share a common ability to protect genes from inappropriate regulatory influences from their neighbours. Insulators possess two main properties: they can block enhancer-promoter communication (enhancer blocker activity), and they can prevent the spread of repressive chromatin (barrier activity). In vertebrates, there is so far one insulator-binding protein, termed CTCF, which confers enhancer blocking in all known chromatin insulators[7,9].

CHROMATIN STRUCTURE AND TRANSCRIPTION CONTROL

The «histone code»

In the eukaryotic nucleus, DNA is packaged as chromatin (2 m of DNA are compacted into a nucleus of about 5 µm diameter). This is obtained by DNA wrapping around basic proteins called histones. The nucleosome is the structural unit of chromatin and consist of 146 bp of DNA wrapped around an octamer of histones (two molecules of each histone H2A, H2B, H3 and H4). In addition of its role in DNA compactation, chromatin represents an additional level of regulation of gene expression[1,10,11].

Chromatin has been traditionally divided into euchromatin and heterochromatin. The former is active (i.e., transcriptionally competent) whereas heterochromatin is transcriptionally inactive. It is necessary to open the compacted chromatin into a relative extended state to initiate transcription so as to expose DNA sequences for interaction with transcription factors. The switching between active and inactive chromatin is closely related to *a)* the activity of histone-modifying enzymes that catalyze post-translational modifications of the histones, and *b)* the activity of chromatin-remodelling complexes that modify nucleosome position.

The histone code refers to enzyme-catalyzed covalent modifications of the histone amino terminal tails (phosphorylation, methylation, ubiquitination, and acetylation) that alter local chromatin organization and ultimately the pattern of gene expression[1,12]. Histone acetylation is probably the most important modification with regard to gene expression and the enzymes involved will be briefly reviewed below. Deregulation and mis-targeting of these histone modifications contributes to the development of several malignancies[13-15]. How this code is established, read, and inherited is the subject of intense investigation, and there are numerous excellent reviews on the histone code[11-13].

DNA methylation and gene expression

In approximately 98% of the human genome the dinucleotide CpG is methylated in the cytosine (i.e., 5-methyl-citosine). This methylation state is inherited by daughter cells after division by the activity of DNA methyltransferases. However, the frequency of the CpG dinucleotides occur 4-5 times less frequently than expected from base composition, except in the so-called CpG islands, regions 1-2 kb long with CpG at high frequency (above 50%) and in unmethylated form. CpG islands are overrepresented in promoters: about 50% of human genes carry CpG islands in their 5' regulatory regions[16].

Methylation of the CpG islands usually has gene repression effects. The mechanism by which DNA methylation can interfere with transcription is to prevent the binding of basal transcription machinery or transcription factors. Examples of permanent gene repression due to hypermethylation are the X chromosome inactivation or genomic imprinting. Also, many tumor suppressor genes have been found to be hypermethylated and thus silenced in human cancer[14].

HOW THE TRANSCRITION OF A GENE IS INITIATED

In most cases, transcription initiation is triggered by one or several transcription factors, following this sequence (summarized in figure 1B):

a) Binding of specific transcription factors to enhancers and/or to regulatory sequences upstream of the transcription start site.

b) Opening of the chromatin through the recruitment of proteins generically termed coactivators. Similarly, corepressors will close the chromatin into inactive state.

c) Binding of Mediator complexes that bridge the transcription factors and the RNAPII holoenzyme.

d) Assembly of the preinitiation complex composed of RNAPII and general transcription factors at the transcription start site.

e) Initiation of transcription and subsequent transcription elongation.

Activators of transcription

There is a subset of genes, the «housekeeping» genes, which expression is constitutive in most cell types and include those for some cytoskeletal protein, pivotal enzymes of the metabolism, ribosomal proteins, etc. Most genes, however, are only expressed in particular cell types, cell cycle phase, developmental stage or in response to extracellular signals. There are several thousands of transcription factors encoded by the mammalian genome: an estimated 5-10% of human genes encode regulatory proteins. These regulatory proteins are usually present in very small amounts in a cell, but their levels can increase dramatically in response to environmental signals. Any given promoter will typically have its own array of binding sites for transcriptional activators and repressors, and many have also enhancers or silencers. The concerted action of these factors will ensure that the gene is only transcribed in the proper cell type(s), at the proper time during development and in response to the proper stimuli. Transcription factors can be activators, which stimulate transcription initiation by recognizing target sites in promoter elements or enhancers[2,7]. Similarly, there are also transcription repressors, which mediate the down-regulation of a previously active gene. Some transcription factors

which regulate the expression of genes involved in the control of proliferation, differentiation or apoptosis appear deregulated in tumors.

Remodelling and opening of the chromatin

Recruitment of coactivator complexes, to the target gene is a critical step for transcription initiation. The coactivators can be divided into two classes:
a) ATP-dependent chromatin-remodelling complexes. They use energy to enable access to nucleosomal DNA by altering the structure, composition and positioning of nucleosomes. Eukaryotes contain at least five families of chromatin remodellers, being the best studied the SWI/SNF and ISWI families[17,18]. They twist and slide nucleosomes, exposing or occluding local DNA to interactions with transcription factors[13].
b) Histone-modifying complexes, which add or remove covalent modifications, such as acetylation, methylation, phosphorylation, and ubiquitination from histones[12]. Acetylation is the best known mechanism so far. Histone acetyltransferases (HAT) activity can increase the accessibility of transcription factors to DNA by neutralizing the positive charge of Lys residues, reducing the compaction of nucleosomal array, disrupting internucleosomal interactions made via the histone tails, or by recruiting additional transcription factors through the histone code mechanism. Thus, activators together with coactivators regulate gene expression by opening the chromatin locally and allowing the access of various transcription factors to nucleosomal DNA. Conversely, histone deacetylases (HDAC) activity results in gene repression. Deacetylation of histones by HDACs diminishes accessibility for transcription factors, giving rise to a closed gene silenced heterochromatin structure. HAT and HDACs are part of large multiprotein complexes involved in transcriptional activation or repression, respectively[10,14].

Mediator

The recruitment of the Mediator Complex, links transcriptional regulators to RNAPII and general transcription factors[19,20]. Mediator (TRAP/ARC/PC2, now termed only Med) is a large (about 1 MDa, 22-28 subunits) protein complex that serves as a bridge between the RNAPII complex and the activators and repressors that convey signals from regulatory elements in the distal promoter as well as enhancers[21].

RNA polymerase II and assembly of the preinitiation complex

RNAPII comprises 12 polypeptide components with a combined molecular weight > 500 kDa[21]. For RNAPII to be engaged in transcription, a pre-initiation complex must be assembled at the transcription start site. Besides RNAPII, it consists of a set of evolutionarily conserved general transcription factors: TFIIA, TFIIB, TFIID, TFIIE, TFIIF and TFIIH. These factors position RNAPII at the transcription start site and unwind a portion of the double stranded DNA to allow access to the template strand[2,21]. The initial contact is made by TFIID, which is a complex made up of the TATA-binding protein (TBP) and at least 12 TBP-associated factors or TAFs. TBP is a sequence-specific protein that binds to the TATA box of DNA forming a platform onto which the remainder of the initiation complex can be assembled[4]. After TFIID has attached to the core promoter, the pre-initiation complex is formed by attachment of the remaining general transcription factors.
The final step in assembly of the initiation complex is the addition of phosphate groups to the C-terminal domain (CTD) of the largest subunit of RNA polymerase II[22]. In mammals, this domain consists of 52 repeats of the seven-amino-acid sequence Tyr-Ser-Pro-Thr-Ser-Pro-Ser, and two of these serines can be phosphorylated. Thus the CTD gets heavily phosphorylated, causing a substantial change in the ionic properties of the RNAPII. Once phosphorylated, the RNAPII leaves the pre-initiation complex and begin synthesizing RNA. Thus, phosphorylated RNAPII marks transcription elongation.
Notably, microRNAs that regulate mRNA transcription have been recently discovered. miRNAs control RNAPII transcription by targeting transcriptional activators and repressors, general factors, RNAPII itself and chromatin[23].

TRANSCRIPTIONAL REGULATION AND CANCER

An important fraction of transcription factors have functions related to the control of cell proliferation and differentiation. Many transcription factors get activated (i.e., competent for transactivation) by phosphorylation by either receptor kinases or intracellular kinases that, in turn are activated by growth factors and cytokines. For example, SMAD transcription factors (usually transcriptional repressors) transduce signals from the TGFβ and BMP receptors, STAT factors transduce signal from many interleukin receptors, CREB from receptors generating cAMP, etc. Finally, the receptors of steroid hormones and retinoids are themselves transcription factors. Not surprisingly, a significant number of protooncogenes encode for transcription factors, and are frequently deregulated, by activating mutations or overexpression, in human tumors. Also, some of the most prominent tumor suppressors are transcription factors. The most frequent human oncogenic transcription factors

TABLE 1. **Transcriptional regulators more prevalent in human cancer**

Transcriptional regulators	Relevant protein domains	Mechanisms of activation/inhibition	Gene rearrangements	Neoplasia type
Oncogenic coactivators				
CBP	HAT	Mutation/deletion	–	Several solid tumors
		Translocation[1]	MOZ-CBP	AML
		Translocation[1]	MLL-CBP	AML
p300	HAT	Mutation	–	Several solid tumors
		Translocation[1]	MLL-p300	AML
β-Catenin	ARM repeats	Deregulated activity	–	Colorectal cancer
Oncogenic transcription factors				
MYC	BR-HLH-LZ	Deregulated activity (overexpression, gene amplification)	–	30-50% of all human tumors
MYC	BR-HLH-LZ	Translocation[2]	IgH-MYC	Burkitt's lymphoma
		Translocation[2]	TCRα-MYC	T-ALL
N-MYC	BR-HLH-LZ	Deregulated expression and gene amplification	–	Neuroblastoma
L-MYC	BR-HLH-LZ	Deregulated expression	–	Lung carcinoma
RUNX1	Runt homology domain	Translocation[1]	RUNX1-ETO	AML
			RUNX1-EVI	AML
			TEL-RUNX1	B-ALL
RARα	Zn finger	Translocation[1]	PML-RARα	APL
			PLZF-RARα	APL
			STAT5b-RARα	APL
MLL	AT Hooks SET domain	Translocation[1]	MLL-AF4	ALL
			MLL-AF9	AML
			MLL-CBP	AML
			MLL-p300	AML
			(many others)	
FLI1	Ets domain	Translocation[1]	FLI1-EWS	Ewing's sarcoma
ERG	Ets domain	Translocation[1]	ERG-EWS	Ewing's sarcoma
PAX family	Homeobox	Translocation[1]	PAX3-FKHR	Alveolar
			PAX7-FKHR	rhabdomyosarcoma
Oncosupressor corepressor				
RB	Pocket domain	Mutation	–	Many sarcomas
		Deletion		and retinoblastomas
Oncosuppresor transcription factor				
p53	Pro rich	Mutation	–	50% of all human tumors
		Deletion		

[1]The translocation generates fusion proteins.
[2]The translocation results in gene deregulation by juxtaposition with TCR or Ig regulatory sequences.
ALL: Acute Lymphoid Leukemia; AML: Acute Myeloid Leukemia; APL: Acute Promyelocytic Leukemia; ARM: Armadillo; BR-HLH-LZ: Basic Region-Helix Loop Helix-Leuzine Zipper; HAT: Histone Acetyl Transferase; Ig: Immunoglobulin; TCR: T-cell receptor.

are summarized in table 1. It must be noted that an additional number of oncogenic transcriptional factors have been found in animal tumors but have not been consistently identified in human cancer yet either in experimental tumorigenesis protocols or as the viral captured oncogene (e.g. v-Fos, v-Jun, PU.1/Spi-1, v-ErbA, v-Ets, v-Rel, v-Myb, etc)[24].

General regulators of transcription as coactivators or corepressors may also function in cancer development. For example, RB (retinoblastoma), the first tumor suppressor gene discovered, is actually a negative regulator of transcription factors of the E2F family. E2F1, 2, and 3 are transcriptional activators of a number of genes involved in cell cycle progression,

but are inactive when bound to RB[25]. The CBP/p300 family of HATs has been found involved in translocations associated with different tumors[26]. Several cancer associated mutations or translocations result in repression of transcription through abnormal recruitment of HDACs, and this is the rationale for the development of HDACs inhibitors as a new class of anticancer therapy[13,15,16].

Deregulation of oncogenic transcription factors give rise to either gain or loss of function because of: *a)* alteration in the cellular localization, *b)* abnormal DNA binding ability or *c)* deregulation of their target genes. Here we will briefly review some of the most important (i.e., more frequently found) in human cancer.

MYC (also called c-MYC) was the first oncogenic transcription factor discovered (1979). MYC belongs to the superfamily of transcription factors with a basic region-helix-loop-helix-leucine zipper domain (BR-HLH-LZ). MYC binds DNA as an heterodimer with the protein MAX. Genome-wide expression and chromatin immunoprecipitation analysis have revealed a big number of MYC target genes (around 1500). Activation of transcription occurs through the recruitment of HAT complexes. However, about 40% of the target genes are down-regulated by MYC, the mechanism for this effect being essentially unknown for most of repressed genes[27-30]. Altogether, these activities contribute to oncogenic transformation. Actually, MYC is found deregulated by chromosomal translocation in practically all Burkitt lymphomas and by other mechanisms not involving translocation in a high fraction of other tumors, ranging between, 30-50%[31].

MLL (ALL1, HRX). The MLL gene, is involved in acute *de novo* leukemias and therapy-related leukemias MLL gene participates in more than 60 translocations with a large number of different partner genes[32]. MLL contains several domains involved in transcription regulation[33,34]. It displays histone methyltransferase activity mediated by the SET domain[12]. MLL seems to activate HOX genes (mostly involved in differentiation) by direct promoter binding and by methylation of histone H3 in Lys 4. Following chromosomal rearrangements, the disruption of MLL function interferes with chromatin remodelling and histone modifications through methylation and converts the truncated MLL in a potent transcriptional activator[35,36].

PML-RARα. In acute promyelocytic leukemia (APL, a subtype of acute myeloid leukemia) the t(15;17) fuses the PML gene with the retinoic acid receptor-α (RARα) gene. PML protein has growth suppression and pro-apoptotic activity. RARα is a member of the nuclear steroid/thyroid hormone receptor superfamily. It functions (forming a dimer with RXR) as a transcriptional activator at retinoid response elements, present in genes involved in myeloid differentiation. In the presence of physiological doses of all-trans-retinoic acid (ATRA), RARα/RXR heterodimer will dissociate from nuclear corepressor complexes and HDAC, and associate with transcriptional activation complexes including CBP/p300 and others. The oncogenic PML-RARα fusion protein has the potential to disrupt both PML- and RARα-dependent pathways[32,35,37]. Leukemia patients with the PML-RARα fusion, are sensitive to ATRA-induced differentiation, being so far the only example of anticancer therapy specifically aimed against a transcription factor. The PML-RARα fusion protein suppresses transcription of ATRA-target genes by recruitment of a HDAC complex, but much higher pharmacological concentrations of ATRA allow the complete dissociation of transcriptional corepressor complexes, which results in the differentiation of leukemic blasts[15,33].

p53. The gene encoding p53 (TP53) is probably the most frequently inactivated tumor suppressor in human cancer (about 50% of all tumors, http://www.p53.iarc.fr/index.html). p53 is a 393 amino acid protein and virtually all mutations found in human cancer (more than 1700 missense mutations) map in the central DNA binding domain of p53 (about 200 amino acids). p53 acts as a «guardian of the genome»: its levels dramatically increase in response to genomic damage and other stress stimuli and triggers cell cycle arrest and/or apoptosis. Not surprisingly, p53 target genes (more than 200) include cell cycle inhibitors and proaopototic mitochondrial proteins, as well as DNA repair proteins. Thus, tumor cells without p53 function are prone to grow despite the chemotherapy or suboptimal growth conditions[38,39].

In face of the evidence that increased activity of these and other transcription factors play a pivotal role in tumorigenesis, transcriptional regulation is becoming an important target in cancer therapy. Thus, HDAC inhibitors, new retinoids and antagonists for nuclear receptors, inhibitors for MYC-MAX binding, p53 stabilizers, etc are being tested. New high throughput screening procedure will surely render valuable anticancer drugs targeting oncogenic transcriptional regulators.

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References

1. Sims RJ, 3rd, Mandal SS, Reinberg D. Recent highlights of RNA-polymerase-II-mediated transcription. Curr Opin Cell Biol. 2004;16:263-71.
2. Szutorisz H, Dillon N, Tora L. The role of enhancers as centres for general transcription factor recruitment. Trends Biochem Sci. 2005;30:593-9.
3. Fukue Y, Sumida N, Nishikawa J, Ohyama T. Core promoter elements of eukaryotic genes have a highly distinctive mechanical property. Nucleic Acids Res. 2004;32:5834-40.
4. Brown T. Assembly of the Transcription Initiation Complex. Genomes 3: Garland Science; 2006.
5. Kadonaga JT. The DPE, a core promoter element for transcription by RNA polymerase II. Exp Mol Med. 2002;34:259-64.
6. Mellor J. The dynamics of chromatin remodeling at promoters. Mol Cell. 2005;19: 147-57.
7. West AG, Fraser P. Remote control of gene transcription. Hum Mol Genet. 2005; 14:101-11.
8. Dean A. On a chromosome far, far away: LCRs and gene expression. Trends Genet. 2006;22:38-45.
9. Ohlsson R, Renkawitz R, Lobanenkov V. CTCF is a uniquely versatile transcription regulator linked to epigenetics and disease. Trends Genet. 2001;17:520-7.
10. Li YJ, Fu XH, Liu DP, Liang CC. Opening the chromatin for transcription. Int J Biochem Cell Biol. 2004;36:1411-23.
11. Khorasanizadeh S. The nucleosome: from genomic organization to genomic regulation. Cell. 2004;116:259-72.
12. Shilatifard A. Chromatin modifications by methylation and ubiquitination: implications in the regulation of gene expression. Annu Rev Biochem. 2006;75:243-69.
13. Santos-Rosa H, Caldas C. Chromatin modifier enzymes, the histone code and cancer. Eur J Cancer. 2005;41:2381-402.
14. Gibbons RJ. Histone modifying and chromatin remodelling enzymes in cancer and dysplastic syndromes. Hum Mol Genet. 2005;14:85-92.
15. Minucci S, Pelicci PG. Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. Nat Rev Cancer. 2006;6:38-51.
16. Herranz M, Esteller M. New therapeutic targets in cancer: the epigenetic connection. Clin Transl Oncol. 2006;8:242-9.
17. Klochendler-Yeivin A, Muchardt C, Yaniv M. SWI/SNF chromatin remodeling and cancer. Curr Opin Genet Dev. 2002;12:73-9.
18. Saha A, Wittmeyer J, Cairns BR. Chromatin remodelling: the industrial revolution of DNA around histones. Nat Rev Mol Cell Biol. 2006;7:437-47.
19. Kornberg RD. Mediator and the mechanism of transcriptional activation. Trends Biochem Sci. 2005;30:235-9.
20. Chadick JZ, Asturias FJ. Structure of eukaryotic Mediator complexes. Trends Biochem Sci. 2005;30:264-71.
21. Asturias FJ. RNA polymerase II structure, and organization of the preinitiation complex. Curr Opin Struct Biol. 2004;14:121-9.
22. Meinhart A, Kamenski T, Hoeppner S, Baumli S, Cramer P. A structural perspective of CTD function. Genes Dev. 2005;19: 1401-15.
23. Goodrich JA, Kugel JF. Non-coding-RNA regulators of RNA polymerase II transcription. Nat Rev Mol Cell Biol. 2006;7: 612-6.
24. Pierotti M, Frattini M, Sozzi G, Croce C. Oncogenes. Cancer Medicine 7. London: BC Decker Inc; 2006. p. 68-84.
25. Frolov MV, Dyson NJ. Molecular mechanisms of E2F-dependent activation and pRB-mediated repression. J Cell Sci. 2004; 117:2173-81.
26. Iyer NG, Ozdag H, Caldas C. p300/CBP and cancer. Oncogene. 2004;23:4225-31.
27. Dang CV, O'Donnell KA, Zeller KI, Nguyen T, Osthus RC, Li F. The c-Myc target gene network. Semin Cancer Biol. 2006; 16:253-64.
28. Adhikary S, Eilers M. Transcriptional regulation and transformation by Myc proteins. Nat Rev Mol Cell Biol. 2005;6:635-45.
29. Lutz W, Leon J, Eilers M. Contributions of Myc to tumorigenesis. Biochim Biophys Acta. 2002;1602:61-71.
30. Grandori C, Cowley SM, James LP, Eisenman RN. The Myc/Max/Mad network and the transcriptional control of cell behavior. Annu Rev Cell Dev Biol. 2000;16:653-99.
31. Nesbit CE, Tersak JM, Prochownik EV. MYC oncogenes and human neoplastic disease. Oncogene. 1999;18:3004-16.
32. Camos M, Colomer D. Molecular biology in acute leukemia. Clin Transl Oncol. 2006;8:550-9.
33. Scandura JM, Boccuni P, Cammenga J, Nimer SD. Transcription factor fusions in acute leukemia: variations on a theme. Oncogene. 2002;21:3422-44.
34. Daser A, Rabbitts TH. The versatile mixed lineage leukaemia gene MLL and its many associations in leukaemogenesis. Semin Cancer Biol. 2005;15:175-88.
35. Willman CL, Hromas RA. Genomic Alterations and Chromosomal Aberrations in Human Cancer. Cancer Medicine 7. London: BC Decker Inc; 2006. p. 104-34.
36. Slany RK. When epigenetics kills: MLL fusion proteins in leukemia. Hematol Oncol. 2005;23:1-9.
37. Grimwade D, Lo Coco F. Acute promyelocytic leukemia: a model for the role of molecular diagnosis and residual disease monitoring in directing treatment approach in acute myeloid leukemia. Leukemia. 2002;16:1959-73.
38. Oren M. Decision making by p53: life, death and cancer. Cell Death Differ. 2003; 10:431-42.
39. Levine AJ, Hu W, Feng Z. The P53 pathway: what questions remain to be explored? Cell Death Differ. 2006;13:1027-36.