CLINICAL MEDICINE & PHARMACOLOGY

CMP

Review article

https://doi.org/10.70731/d74qh728

Abnormal Expression of Transcription Factor IIIA in Tumors and Target Therapy Potential Application for Transcription Factor IIIA

Jing Wang [1,2], **Faqing Tang** [1,*]

Received 3 May 2026

Revised 7 June 2026

Accepted 26 July 2026

Published 31 July 2026

ISSN 2760-1757 (Online)
ISSN 2760-3288 (Print)

© 2026 The Author(s)
Published by Jandoo Press Co., Ltd.

This article is licensed under the terms and conditions of the Creative Commons Attribution (CC BY) license: http://creativecommons.org/licenses/by/4.0/

Abstract: Transcription factor III a (TFIIIA), as one of the specific transcription factor members of RNA polymerase III, plays an important role in guiding the transcription of 5S rRNA genes by RNA polymerase III. This article elaborates on the special structure and function of TFIIIA, and introduces the synergistic effect of homologous transcription factors TFIIIB and TFIIIC in the process of 5S rRNA gene transcription guided by RNA polymerase III. It also discusses the relationship between RNA polymerase III transcription activity and the product 5SrRNA and the occurrence and development of tumors. The abnormal expression of most transcription factors is involved in the occurrence and development of various cancers, and 20% of the oncogenes discovered are transcription factors. In order to explore the transcription factor TFIIIA as a tumor therapy target, this article probe the strategy in which transcription factors are used as tumor therapy targets based on discussing TFIIIA structure and function, including its expression and degradation, interaction with cofactors/proteins, and dynamic changes in its binding to DNA.

Keywords: Transcription factor; TFIIIA; 5S rRNA; Tumor; Target therapy

Introduction

Transcription factor IIIA (TFIIIA) is a eukaryotic transcription factor that was purified and extracted from Xenopus laevis oocytes, it is widely expressed in various tissues and organs. Subsequently, some reseaches isolated a new cDNA (GTF3A) from the human genome, located it on chromosome band 13q12.3→q13.1, and found that it is highly homologous to Xenopus transcription factor IIIA (GTF3A). It is believed that this human cDNA shares the same structure and function as Xenopus derived GTF3A [2]. Later, it was discovered that TFIIIA homologous sequences exist in various organisms, such as yeast, Arabidopsis, spotted catfish, and mice. The primary protein sequence of this transcription factor is generally poorly conserved, but all known TFIIIA proteins have a similar structure with C-terminal domain, the C-terminal domain is consist of nine consecutive Cys2-His2 zinc finger domains [3]. In the process of human evolution, human TFIIIA retains the common conserved transcriptional activation signal (TAS), nuclear localization signal (NSL), and nuclear output signal (NES), but loses the initial Met and accompanying conserved residues in the N-terminal region [4]. Although the conservation of the original protein sequence is poor during the evolution of eukaryotes, TFIIIA has a large number of zinc finger domains and extended DNA recognition sequences, making it highly affinity and specific for binding to DNA and RNA [5]. According to further research reports, TFIIIA is identified as one of the RNApolIII specific transcription factors that are responsible for the transcription of the 5SrRNA gene [6,7]. This article systematically introduces the molecular structure and function of TFIIIA, elucidates the synergistic effect and mechanism between TFIIIA and homologous transcription factors TFIIIB/TFIIIC, explores the relationship between TFIIIA-mediated signaling network and tumor occurrence and development, and explores its feasibility as a cancer treatment target from the perspective of transcription factors.

[1] Hunan Key Laboratory of Oncotarget Gene and Clinical Laboratory, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University & Hunan Cancer Hospital, Changsha 410013, China; [2] Department of Clinical Laboratory, The Central Hospital of Xiangtan, Xiangtan 411100, China.
*Corresponding author. Email: tangfq@hnca.org.cn

Structure and Function of TFIIIA

TFIIIA, as a classic zinc finger protein, has nine repeated zinc finger domains. The N-terminus of the zinc finger structure is a region composed of approximately 280 amino acids, which binds to DNA/RNA but does not encode transcription and is considered a binding domain. The C-terminus of the zinc finger structure is a region of approximately 65 amino acids, it is important for activating gene transcription. The C-terminus is considered a transcription factor activation domain [8,9]. The specific binding of TFIIIA to the imprinting control region (ICR) sequence of the 5SrRNA gene depends on the zinc finger structure. The N-terminal zinc finger (Zf)1-3 is a key structural domain for specific binding to the C-box of the ICR of the 5SrRNA. Among them, Zf3 has the ability to specifically recognize 5SrDNA [10]; Zf7-9 binds to the A-box of ICR, Zf5 binds to the intermediate element, while Zf4 and 6 bind to small grooves that run through the A-box, intermediate element, and C-box regions, respectively. TFIIIA binds to 5SrRNA, requiring a zinc finger structure Zf 4-7 [11-14]. Obviously, due to the presence of the TFIIIA zinc finger domain, it can specifically bind to 5SrDNA and has a high affinity for 5SrRNA. After binding to 5SrRNA, TFIIIA forms a 7SRNP complex, which can cross the nuclear membrane and transport 5SrRNA from the nucleolus to the cytoplasm for storage in preparation for ribosome assembly, thus forming a TFIIIA mediated 5SrRNA nucleolar cytoplasmic transport [15].

TFIIIA in all organisms is encoded by a single gene, and it has a unique basic function of driving 5SrRNA gene expression. TFIIIA binds to the ICR region (nucleotides +43 to +96) of 5S rRNA gene to initiate transcription, which is the first step in the assembly of transcription complexes (TFIIIA, TFIIIC, TFIIIB, and RNApolIII). TFIIIC then binds to TFIIIA and TFIIIB and stabilize them, and finally TFIIIB completes the assembly of the transcription initiation complex. The entire process is indispensable [15-17]. TFIIIA is abundant in amphibian oocytes and highly expressed during the reproductive stage of plants, promoting the accumulation of 5SrRNA and facilitating ribosome biogenesis to meet developmental needs. However, TFIIIA in somatic cells remains at a low level, indicating that TFIIIA is tightly regulated to maintain a balance in differentiated somatic cells [16,18,19]. TFIIIA combines the dual functions of 5S rDNA and 5S rRNA, indicating the existence of a negative feedback self-regulation model for 5S rRNA transcription [20]. Some studies reported expression regulation of TFIIIA, such as TFIIIA is maintained in plants through transcriptional level regulation, TFIIIA protein alternative splicing, and NMD degradation pathway [19]. The transcriptional availability of TFIIIA in Xenopus laevis oocytes is limited by the accumulation of nuclear RPL5, a nucleic acid protein interaction network involving 5SrDNA, 5SrRNA, TFIIIA, and riboprotein L5, which contributes to the steady-state control of ribosome assembly [4]. In this transcription process that are influenced by multiple factors, the ultimate destination is ribosome biogenesis, and coordinated ribosome biogenesis is a key factor in cell biology. The synthesis of ribosomal RNA (via RNApolI and RNApolIII) and proteins (via RNApolII) requires high regulation [21].

Homologous Transcription Factor TFIIIB/TFIIIC of TFIIIA

TFIIIB/TFIIIC are specific transcription factors of RNApolIII homologous to TFIIIA, they play an important role in the occurrence and development of various tumors. TFIIIB is a complex composed of three subunits, TATA binding protein (TBP), Brf1 TFIIB related factor 1 (Brf1), and Bdp1, it is responsible for recruiting RNApolIII and activating the RNApolIII pre-activation complex that regulates the transcription process of RNApolIII. Its promoting effect on RNApolIII transcription further mediates cell transformation and tumorigenesis, which make it a target for many cancer regulatory proteins. It has been reported in both colon cancer and liver cancer that the oncogenic signaling pathway JNK mediates upregulation of TBP expression, and overexpression of TBP induces cell proliferation and contributes to cell transformation. For TBP regulating targets, some studies have found that overexpression of TBP can induce transcription of VEGFA and promote cell migration and tumor angiogenesis, thereby promoting tumor development [22-24]. Brf1 is considered as a new biomarker for live cancer and breast cancer. Stimulated by alcohol in liver cancer and breast cancer, alcohol can induce the activation of c-jun and ER α targets, significantly increase the expression of Brf1, and thus induce the increase of RNApolIII transcription level, which plays a crucial role in cell transformation and tumorigenesis [25-27]. The active ingredient Bdp1 is involved in the recruitment of RNApol III and the opening of DNA promoters, playing a crucial role in the transcriptional initiation process of RNApol III [28,29]. In summary, TFIIIB is a key component regulating RNApolIII transcription and plays an important role in cell transformation and tumorigenesis.

TFIIIC is a conserved six subunit protein complex composed of sub complexes (τ A and τ B). TFIIIC has unique crystal structure, its molecular structure was determined by chemical cross-linking mass spectrometry. It was found that there is a self interaction between τ 131 of the τ A and τ 138 of the τ B subunits, and their central regions overlap with the binding site of TFIIIB. This can affect the formation of RNApolIII pre-triggered complexes through both self interaction and interaction with TFIIIB, providing an important platform for tRNA transcriptional regulation [30]. In addition, TFIIIC also contains a special TOR signaling motif that can be associated with mTOR and TFIIIC being recruited into RNApolIII transcribed genes. mTOR kinase is located in tRNA and 5S rRNA genes, providing opportunities for direct regulation. Therefore, the process of RNA polIII synthesis of tRNA and 5S rRNA is to some extent regulated by the mTOR pathway [31,32]. However, compared to TFIIIB, TFIIIC has weaker binding to tRNA genes and has a relatively limited impact on RNApolIII transcription levels.

Network Mediated by TFIIIA Transcript 5SrRNA

5SrRNA is a product of TFIIIA specific transcription. 5SrRNA, as the smallest RNA component in the large ribosome subunit, is located at the junction between the large ribosome subunit (60S in eukaryotes) and the small ribosome subunit (40S in eukaryotes), and is part of the central protrusion. Its secondary structure consists of five spirals, four rings, and a hinge folded into a "Y-shaped" structure. 5SrRNA is essential for the normal translation of most ribosomes. Although its exact function in ribosomes is not yet clear, 5SrRNA is believed to play a critical role in protein RNA and RNA-RNA interactions within the ribosome. Ribosomal biogenesis is considered a key driving factor in tumorigenesis, and its dysregulation can further affect cancer progression [33-35]. In terms of protein RNA interactions, It is verified that the 5SRNP complex that is composed of RPL5, RPL11, and 5SrRNA, is the central regulator of tumor suppressor gene p53 homeostasis. In short, in the MDM2 (murine double minute 2)-p53 regulatory pathway, 5SRNP inactivates MDM2 by binding to it, blocking MDM2-mediated p53 ubiquitination and releasing and activating P53, which plays an important regulatory role in tumor suppression [36-38]. 5SRNP complex is considered an ideal target for cancer and ribosomal disease treatment. The three major components that make up the 5SRNP complex all play important roles, but the effect of 5SrRNA is relatively limited compared to RPL5/RPL11 [38,39]. This is because cytoplasmic nucleolar transport function of 5SrRNA mediated by TFIIIA provides sufficient 5SrRNA storage pools for the assembly of 5SRNP. Therefore, the newly synthesized 5SrRNA from TFIIIA has limited and delayed impact on this process [40].

The Role of Transcription Factors in Biological Development and Carcinogenesis

During normal embryonic development, stem cells differentiate into characteristic cell types, and the acquisition of these characteristics depends on the pre-existing morphological gradient of genes and activation of TFs. During the occurrence and development of tumors, the transformation of cells requires a change in cellular identity. Functional differentiated cells lose the characteristics obtained from differentiation, and acquire progenitor cell characteristics during dedifferentiation [41]. The molecular mechanisms of the cells during normal embryonic development are relatively conserved and in a dynamic equilibrium. However, when tumors disrupt this equilibrium, previously suppressed genes are reactivated, and the continuous accumulation of gene mutations leads to uncontrolled cell proliferation and misidentification of cell identity. Both in normal development and cancer transformation, Epithelial-mesenchymal transition (EMT), progenitor cell proliferation, and cell migration are shared biological processes, but the different coordination of these events leads to different developmental outcomes for cells. During development, EMT is involved in neural crest development, progenitor cell proliferation is related to stem cell maturation and fertilization, and the formation of fertilized eggs and the migration of blastocysts to the uterine wall are related to cell migration. During the development of tumors, EMT is involved in tumor metastasis, self-renewal, and immune escape. And EMT even affects the proliferation of progenitor cells, while the migration of cancer cells from organs/blood vessels to surrounding tissues involves cell migration [42]. TFs regulate transcription in almost every process of an organism. On the one hand, they regulate a wide range of biological processes to maintain homeostasis, and on the other hand, their dysregulation is the core that affects the occurrence and development of various cancers.

TFs account for nearly 20% of discovered oncogenes, such as the high mobility group protein (HMG) family, which can regulate the transcription of oncogenes and metastasis related genes such as c-FOS, BCL3, N-cadherin, JunB, and c-Jun [43]. There are also some TFs associated with EMT, such as snail, slug, Twist, and FoxD3 [44, 45]. Transcriptional regulation is often convergence point of oncogenic signals, and abnormal gene expression is a major characteristic that leads to the occurrence and development of tumors, searching transcription targeted drugs to correct transcriptional abnormalities is an important means of tumor treatment [46]. A better understanding to the precise functions (expression, degradation pathways, and protein/protein interactions) and dynamic binding modes of transcription factors provides new possibilities for transcription factors as targets for cancer treatment.

Clinical Application of Targeting Transcription Factors in Various Cancers

In various tumors, the direct mechanisms that alter TF activity include chromosomal translocation, gene amplification or deletion, point mutations, and changes in expression levels, while indirect mechanisms include non coding DNA mutations that affect TF binding [47]. TFs often bind to DNA to regulate gene transcription. The interactions between TFs and DNA binding sites are complex and diverse, playing an important role in gene regulatory networks [48]. Next, we introduce several classic pathways for targeting TFs in various types of cancer.

Targeted TFs at expression levels

The TFs, like other proteins, are regulated by transcriptional activators or repressors in their expression. In the context of leukemia, the HOXA TF cluster is abnormally expressed under the regulation of MLL (mixed lineage leukemia, MLL) complex, and this TF expression regulatory mechanism has significant application effects in leukemia therapy [49]. In clinical practice, various protein partners

and inhibitors corresponding to leukemia have been developed, such as HMT, Menin/LEDGF inhibitors, WDR5/MLL interaction inhibitors, etc., which suppress the activity expression of HOXA5-10 TFs by targeting TFs to achieve therapeutic goals [50-53]. Another widely studied family of oncogenic transcription factors is the MYC gene family, which is associated with dysregulation of c-MYC TFs in various cancers, immune disorders, and hematological diseases. It is mainly regulated by epigenetics including gene amplification, translocation, promoter polymorphism or mutation [54], and it has been found that the expression of these TFs is influenced by the activity of the c-MYC promoter. Based on this theory, drugs that inhibit the activity of the c-MYC promoter, such as BRD4 inhibitors and HDAC inhibitors, have been developed. These drugs achieve therapeutic goals by negatively regulating the expression of c-MYC through inhibiting the activity of the c-MYC promoter [55,56].

Targeting TFs at protein degradation level

The degradation of TFs is generally achieved through ubiquitin proteasome or glycosylation pathways, which modify the stability of TF proteins. The targeted therapy for protein degradation fundamentally involves cutting off pathways to affect the expression levels of TFs [57]. There are many target therapies targeting the degradation of TF proteins, such as the induction of transcription factor c-MYB degradation by tebuconazole (Vermox), which is a safe and novel treatment for acute myelocytic leukemia (AML) [58], and BCL6 degradation compounds that chemically induce BCL6 oncogenic TF degradation to treat lymphoid malignancies [59]. Small molecule MVI compounds developed based on protein knockout system can induce the degradation of TF NOTCH1 protein to treat breast cancer (especially triple negative breast cancer), leukemia, brain tumor, etc. [60]; PROTAC, which targets the ubiquitination and degradation of Smad3 protein, can prevent renal fibrosis [61].

Targeting TF protein-protein interactions

Some TF proteins do not exist as monomers and have the characteristics and background of protein-protein interactions. Due to their often paired interactions, they regulate each other to form a steady-state equilibrium. The classic P53/MDM2 is related to protein degradation processes, and its tumor suppressor p53 were the first TF that was discovered to be regulated at PPI (protein-protein interaction). Various inhibitors that target to P53/MDM2 interaction have been developed in clinical practice, such as nutans, spiroindoles, isoquinone, and piperidone analogs, which have broad application prospects in cancer treatment [62-64]. Another classic example is Keap1/Nrf2. Keap1 mediates the ubiquitination of Nrf2, which is the main regulator of antioxidant response. The development of PPII drugs to block the interaction between Keap1 and Nrf2 provides a new strategy for novel antioxidant, anti-inflammatory, and anticancer effects [65,66].

Targeting TF protein binding to DNA

DNA itself is a target for anti-tumor therapy, and targeting specific sequences of DNA prevents TFs from binding to specific DNA sequences, which is regulated at the level of TF protein binding with DNA . DNA alkylating drugs are targeted drugs that are developed based on this principle. DNA alkylation leads to maximum DNA damage, resulting in the death of cancer cells or other circulating cells, such as polymyxin, platinum drugs, CC-1065, ET743, etc., which interfere with TF/DNA binding and rapidly block transcription. Many of these drugs have strong anti-tumor activity and have even been applied in clinical trials [67-70]. In addition, there are also some inhibitors of TF binding to DNA that insert between two consecutive base pairs to affect the helical spatial structure or bind to the main groove or small slot of the DNA helix. By competitive binding, they alter the spatial structure of DNA to affect its binding to TFs. Compared to DNA alkylation, the damage to DNA is reduced, but the regulatory power of these inhibitors is also quite limited [71-73].

The development of small molecule inhibitors targeting TFs at different levels is due to the advancement of modern chemical technology, which has provided a deeper understanding to TFs through new techniques, making it possible for TFs to serve as cancer treatment targets.

Conclusions and Prospects

RNApolIII, as an important polymerase, regulates the biosynthetic ability of cells by translating U6snRNA, tRNAs, and 5SrRNA [74,75]. Dysregulation of RNApolIII transcription induces malignant transformation of cells and is a key factor in the development of cancer. The three key TFs of RNApolIII are TFIIIA, TFIIIB, and TFIIIC. Current researches on TFIIIB and TFIIIC show that they are closely related to the occurrence and development of cancer. The clear function of TFIIIA TF is to mediate the transcription of 5SrRNA genes. As a classic zinc finger protein, TFIIIA can not only bind to DNA, but also to RNA during plant reproductive stages, and has extremely rich protein accumulation during oocyte embryonic development. However, TFIIIA expression is extremely limited in human somatic cells, and the 5S rRNA nucleolar cytoplasmic transport function mediated by TFIIIA largely satisfies the product requirements of TFIIIA. The TFIIIA activity in normal cells is relatively low. The role of TFs in normal development and tumorigenesis is generally two-sided functions. On the one hand, they regulate a wide range of biological processes to maintain homeostasis, and on the other hand, their dysregulation is the core that affects the occurrence and development of various cancers. Since TFIIIA is widely expressed in various tissues and organs, it is an essential specific transcription factor for RNApolIII transcription. What impact does its dysregulation have on the occurrence and development of cancer? Does it also have the opportunity to become a new target for cancer treatment by drawing on the expression, degradation, and interaction

mechanisms of general transcription factors with other proteins?

Funding: This work was supported in part by Major Scientific and Technological Innovation Project of Hunan Province (2021SK1020-4); Changsha Science and Technology Project (20210126-1001、20201228-1005).

Data Availability: All data generated or analyzed during this study are included in this article and its supplementary Data.

Author Contributions: JW prepared and wrote the manuscript. FQT supervised the project and revised the manuscript. All authors read and approved the final manuscript.

Competing Interests: Author FQT serves on the editorial board of this journal but had no role in the peer review or decision-making

process for this article. Referneces

1. Engelke, D.R., et al.,Specific interaction of a purified transcription factor with an internal control region of 5S RNA genes.Cell, 1980.19(3): p. 717-28. https://doi.org/10.1016/S0092-8674(80)80048-1
2. Arakawa, H., et al.,Molecular cloning, characterization, and chromosomal mapping of a novel human gene (GTF3A) that is highly homologous to Xenopus transcription factor IIIA.Cytogenet Cell Genet, 1995.70(3-4): p. 235-8. https://doi.org/10.1159/000134041
3. Mathieu, O., et al.,Identification and characterization of transcription factor IIIA and ribosomal protein L5 from Arabidopsis thaliana.Nucleic Acids Res, 2003.31(9): p. 2424-33. https://doi.org/10.1093/nar/gkg335
4. Hanas, J.S., et al.,cDNA cloning, DNA binding, and evolution of mammalian transcription factor IIIA.Gene, 2002.282(1-2): p. 43-52.
5. Layat, E., A.V. Probst, and S. Tourmente,Structure, function and regulation of Transcription Factor IIIA: From Xenopus to Arabidopsis.Biochim Biophys Acta, 2013.1829(3-4): p. 274-82. https://doi.org/10.1016/j.bbagrm.2012.10.013
6. Shastry, B.S.,Transcription factor IIIA (TFIIIA) in the second decade.J Cell Sci, 1996.109 (Pt 3): p. 535-9.
7. Birkenmeier, E.H., D.D. Brown, and E. Jordan,A nuclear extract of Xenopus laevis oocytes that accurately transcribes 5S RNA genes.Cell, 1978.15(3): p. 1077-86. https://doi.org/10.1016/0092-8674(78)90291-X
8. Darsillo, P. and P.W. Huber,The use of chemical nucleases to analyze RNA-protein interactions. The TFIIIA-5 S rRNA complex.J Biol Chem, 1991.266(31): p. 21075-82.
9. Fairall, L. and D. Rhodes,A new approach to the analysis of DNase I footprinting data and its application to the TFIIIA/5S DNA complex.Nucleic Acids Res, 1992.20(18): p. 4727-31. https://doi.org/10.1093/nar/20.18.4727
10. Del Rio, S. and D.R. Setzer,The role of zinc fingers in transcriptional activation by transcription factor IIIA.Proc Natl Acad Sci U S A, 1993.90(1): p. 168-72. https://doi.org/10.1073/pnas.90.1.168
11. Theunissen, O., et al.,RNA and DNA binding zinc fingers in Xenopus TFIIIA.Cell, 1992.71(4): p. 679-90. https://doi.org/10.1016/0092-8674(92)90601-8
12. Ryan, R.F. and M.K. Darby,The role of zinc finger linkers in p43 and TFIIIA binding to 5S rRNA and DNA.Nucleic Acids Res, 1998.26(3): p. 703-9. https://doi.org/10.1093/nar/26.3.703
13. Shastry, B.S.,Transcription factor IIIA (TFIIIA): an update.Experientia, 1993.49(10): p. 831-5. https://doi.org/10.1007/BF01952592
14. Theunissen, O., F. Rudt, and T. Pieler,Structural determinants in 5S RNA and TFIIIA for 7S RNP formation.Eur J Biochem, 1998.258(2): p. 758-67. https://doi.org/10.1046/j.1432-1327.1998.2580758.x
15. Bieker, J.J., P.L. Martin, and R.G. Roeder,Formation of a rate-limiting intermediate in 5S RNA gene transcription.Cell, 1985.40(1): p. 119-27. https://doi.org/10.1016/0092-8674(85)90315-0
16. Seifart, K.H., et al.,Purification of human transcription factor IIIA and its interaction with a chemically synthesized gene encoding human 5 S rRNA.J Biol Chem, 1989.264(3): p. 1702-9.
17. Weser, S., et al.,Assembly and isolation of intermediate steps of transcription complexes formed on the human 5S rRNA gene.Nucleic Acids Res, 2003.31(9): p. 2408-16. https://doi.org/10.1093/nar/gkg318
18. Fu, Y., et al.,Alternative splicing of anciently exonized 5S rRNA regulates plant transcription factor TFIIIA.Genome Res, 2009.19(5): p. 913-21. https://doi.org/10.1101/gr.087197.108
19. Layat, E., et al.,Transcript levels, alternative splicing and proteolytic cleavage of TFIIIA control 5S rRNA accumulation during Arabidopsis thaliana development.Plant J, 2012.71(1): p. 35-44. https://doi.org/10.1111/j.1365-313X.2012.05008.x
20. Cassiday, L.A. and L.J. Maher, 3rd,Having it both ways: transcription factors that bind DNA and RNA.Nucleic Acids Res, 2002.30(19): p. 4118-26. https://doi.org/10.1093/nar/gkf535
21. Laferté, A., et al., The transcriptional activity of RNA polymerase I is a key determinant for the level of all ribosome components. Genes Dev, 2006. 20(15): p. 2030-40. https://doi.org/10.1101/gad.386106
22. Johnson, S.A., et al., Increased expression of TATA-binding protein, the central transcription factor, can contribute to oncogenesis. Mol Cell Biol, 2003. 23(9): p. 3043-51. https://doi.org/10.1128/MCB.23.9.3043-3051.2003
23. Zhong, S., J. Fromm, and D.L. Johnson, TBP is differentially regulated by c-Jun N-terminal kinase 1 (JNK1) and JNK2 through Elk-1, controlling c-Jun expression and cell proliferation. Mol Cell Biol, 2007. 27(1): p. 54-64. https://doi.org/10.1128/MCB.01365-06
24. Johnson, S.A.S., et al., Elevated TATA-binding protein expression drives vascular endothelial growth factor expression in colon cancer. Oncotarget, 2017. 8(30): p. 48832-48845. https://doi.org/10.18632/oncotarget.16384
25. Zhong, Q., et al., Tamoxifen represses alcohol-induced transcription of RNA polymerase III-dependent genes in breast cancer cells. Oncotarget, 2014. 5(23): p. 12410-7. https://doi.org/10.18632/oncotarget.2678
26. Yi, Y., et al., Exploring a common mechanism of alcohol-induced deregulation of RNA Pol III genes in liver and breast cells. Gene, 2017. 626: p. 309-318. https://doi.org/10.1016/j.gene.2017.05.048
27. Zhong, Q., et al., The significance of Brf1 overexpression in human hepatocellular carcinoma. Oncotarget, 2016. 7(5): p. 6243-54. https://doi.org/10.18632/oncotarget.6668
28. Gouge, J., et al., Molecular mechanisms of Bdp1 in TFIIIB assembly and RNA polymerase III transcription initiation. Nat Commun, 2017. 8(1): p. 130. https://doi.org/10.1038/s41467-017-00126-1
29. Román-Carraro, F.C., et al., TFIIIB Subunit Bdp1 Participates in RNA Polymerase III Transcription in the Protozoan Parasite

Leishmania major. Biomed Res Int, 2019. 2019: p. 1425281. https://doi.org/10.1155/2019/1425281

30. Male, G., et al., Architecture of TFIIIC and its role in RNA polymerase III pre-initiation complex assembly. Nat Commun, 2015. 6: p. 7387. https://doi.org/10.1038/ncomms8387
31. Kantidakis, T., et al., mTOR associates with TFIIIC, is found at tRNA and 5S rRNA genes, and targets their repressor Maf1. Proc Natl Acad Sci U S A, 2010. 107(26): p. 11823-8. https://doi.org/10.1073/pnas.1005188107
32. Graczyk, D., M. Cieśla, and M. Boguta, Regulation of tRNA synthesis by the general transcription factors of RNA polymerase III - TFIIIB and TFIIIC, and by the MAF1 protein. Biochim Biophys Acta Gene Regul Mech, 2018. 1861(4): p. 320-329. https://doi.org/10.1016/j.bbagrm.2018.01.011
33. Szymanski, M., et al., 5 S rRNA: structure and interactions. Biochem J, 2003. 371(Pt 3): p. 641-51. https://doi.org/10.1042/BJ20020872
34. Slimane, S.N., et al., Ribosome Biogenesis Alterations in Colorectal Cancer. Cells, 2020. 9(11). https://doi.org/10.3390/cells9112361
35. Ciganda, M. and N. Williams, Eukaryotic 5S rRNA biogenesis. Wiley Interdiscip Rev RNA, 2011. 2(4): p. 523-33. https://doi.org/10.1002/wrna.74
36. Miliani de Marval, P.L. and Y. Zhang, The RP-Mdm2-p53 pathway and tumorigenesis. Oncotarget, 2011. 2(3): p. 234-8. https://doi.org/10.18632/oncotarget.228
37. Liu, Y., et al., Ribosomal protein-Mdm2-p53 pathway coordinates nutrient stress with lipid metabolism by regulating MCD and promoting fatty acid oxidation. Proc Natl Acad Sci U S A, 2014. 111(23): p. E2414-22. https://doi.org/10.1073/pnas.1315605111
38. Sloan, K.E., M.T. Bohnsack, and N.J. Watkins, The 5S RNP couples p53 homeostasis to ribosome biogenesis and nucleolar stress. Cell Rep, 2013. 5(1): p. 237-47. https://doi.org/10.1016/j.celrep.2013.08.049
39. Onofrillo, C., et al., The pre-existing population of 5S rRNA effects p53 stabilization during ribosome biogenesis inhibition. Oncotarget, 2017. 8(3): p. 4257-4267. https://doi.org/10.18632/oncotarget.13833
40. Neely, L.S., et al., Identification of a minimal domain of 5 S ribosomal RNA sufficient for high affinity interactions with the RNA-specific zinc fingers of transcription factor IIIA. J Mol Biol, 1999. 291(3): p. 549-60. https://doi.org/10.1006/jmbi.1999.2985
41. Roy, N. and M. Hebrok, Regulation of Cellular Identity in Cancer. Dev Cell, 2015. 35(6): p. 674-84. https://doi.org/10.1016/j.devcel.2015.12.001
42. Huilgol, D., et al., Transcription Factors That Govern Development and Disease: An Achilles Heel in Cancer. Genes (Basel), 2019. 10(10). https://doi.org/10.3390/genes10100794
43. Lim, J.H., et al., Chromosomal protein HMGN1 modulates histone H3 phosphorylation. Mol Cell, 2004. 15(4): p. 573-84. https://doi.org/10.1016/j.molcel.2004.08.006
44. Tepass, U., C. Theres, and E. Knust, crumbs encodes an EGF-like protein expressed on apical membranes of Drosophila epithelial cells and required for organization of epithelia. Cell, 1990. 61(5): p. 787-99. https://doi.org/10.1016/0092-8674(90)90189-L
45. Edelman, G.M. and K.L. Crossin, Cell adhesion molecules: implications for a molecular histology. Annu Rev Biochem, 1991. 60: p. 155-90.
46. Yan, C. and P.J. Higgins, Drugging the undruggable: transcription therapy for cancer. Biochim Biophys Acta, 2013. 1835(1): p. 76-85. https://doi.org/10.1016/j.bbcan.2012.11.002
47. Bushweller, J.H., Targeting transcription factors in cancer - from undruggable to reality. Nat Rev Cancer, 2019. 19(11): p. 611-624. https://doi.org/10.1038/s41568-019-0196-7
48. Badis, G., et al., Diversity and complexity in DNA recognition by transcription factors. Science, 2009. 324(5935): p. 1720-3. https://doi.org/10.1126/science.1162327
49. Kawagoe, H., et al., Expression of HOX genes, HOX cofactors, and MLL in phenotypically and functionally defined subpopulations of leukemic and normal human hematopoietic cells. Leukemia, 1999. 13(5): p. 687-98. https://doi.org/10.1038/sj.leu.2401387
50. Zhang, W., et al., Dot1a-AF9 complex mediates histone H3 Lys-79 hypermethylation and repression of ENaCalpha in an aldosterone-sensitive manner. J Biol Chem, 2006. 281(26): p. 18059-68. https://doi.org/10.1074/jbc.M601903200
51. Zhou, H., et al., Structure-based design of high-affinity macrocyclic peptidomimetics to block the menin-mixed lineage leukemia 1 (MLL1) protein-protein interaction. J Med Chem, 2013. 56(3): p. 1113-23. https://doi.org/10.1021/jm301649m
52. Shi, A., et al., Structural insights into inhibition of the bivalent menin-MLL interaction by small molecules in leukemia. Blood, 2012. 120(23): p. 4461-9. https://doi.org/10.1182/blood-2012-05-429449
53. Karatas, H., et al., High-affinity, small-molecule peptidomimetic inhibitors of MLL1/WDR5 protein-protein interaction. J Am Chem Soc, 2013. 135(2): p. 669-82. https://doi.org/10.1021/ja308415m
54. Trop-Steinberg, S. and Y. Azar, Is Myc an Important Biomarker? Myc Expression in Immune Disorders and Cancer. Am J Med Sci, 2018. 355(1): p. 67-75. https://doi.org/10.1016/j.amjms.2017.09.010
55. Fowler, T., et al., Regulation of MYC expression and differential JQ1 sensitivity in cancer cells. PLoS One, 2014. 9(1): p. e87003. https://doi.org/10.1371/journal.pone.0087003
56. Mazur, P.K., et al., Combined inhibition of BET family proteins and histone deacetylases as a potential epigenetics-based therapy for pancreatic ductal adenocarcinoma. Nat Med, 2015. 21(10): p. 1163-71. https://doi.org/10.1038/nm.3952
57. Desterro, J.M., M.S. Rodriguez, and R.T. Hay, Regulation of transcription factors by protein degradation. Cell Mol Life Sci, 2000. 57(8-9): p. 1207-19. https://doi.org/10.1007/PL00000758
58. Walf-Vorderwülbecke, V., et al., Targeting acute myeloid leukemia by drug-induced c-MYB degradation. Leukemia, 2018. 32(4): p. 882-889. https://doi.org/10.1038/leu.2017.289
59. Kerres, N., et al., Chemically Induced Degradation of the Oncogenic Transcription Factor BCL6. Cell Rep, 2017. 20(12): p. 2860-2875. https://doi.org/10.1016/j.celrep.2017.08.081
60. Ohoka, N., et al., Development of a peptide-based inducer of protein degradation targeting NOTCH1. Bioorg Med Chem Lett, 2017. 27(22): p. 4985-4988. https://doi.org/10.1016/j.bmcl.2017.10.020
61. Wang, X., et al., New strategy for renal fibrosis: Targeting Smad3 proteins for ubiquitination and degradation. Biochem Pharmacol, 2016. 116: p. 200-9. https://doi.org/10.1016/j.bcp.2016.07.012
62. Lemos, A., et al., Medicinal Chemistry Strategies to Disrupt the p53-MDM2/MDMX Interaction. Med Res Rev, 2016. 36(5): p. 789-844. https://doi.org/10.1002/med.21397
63. Nayak, S.K., et al., p53-Mdm2 Interaction Inhibitors as Novel Nongenotoxic Anticancer Agents. Curr Cancer Drug Targets, 2018. 18(8): p. 749-772. https://doi.org/10.2174/1568009618666180102160226

64. Wang, S., et al., Targeting the MDM2-p53 Protein-Protein Interaction for New Cancer Therapy: Progress and Challenges. Cold Spring Harb Perspect Med, 2017. 7(5). https://doi.org/10.1101/cshperspect.a026245
65. Jiang, Z.Y., et al., Discovery of potent Keap1-Nrf2 protein-protein interaction inhibitor based on molecular binding determinants analysis. J Med Chem, 2014. 57(6): p. 2736-45. https://doi.org/10.1021/jm4015279
66. Yasuda, D., et al., Synthesis of Keap1-phosphorylated p62 and Keap1-Nrf2 protein-protein interaction inhibitors and their inhibitory activity. Bioorg Med Chem Lett, 2016. 26(24): p. 5956-5959. https://doi.org/10.1016/j.bmcl.2016.10.070
67. Tanaka, N., Inhibition of transcription by pluramycin and bleomycin. J Antibiot (Tokyo), 1970. 23(11): p. 523-30.
68. Kasparkova, J., et al., Biophysical studies on the stability of DNA intrastrand cross-links of transplatin. Biophys J, 2008. 95(9): p. 4361-71. https://doi.org/10.1529/biophysj.108.136382
69. Chiang, S.Y., et al., Effects of minor groove binding drugs on the interaction of TATA box binding protein and TFIIA with DNA. Biochemistry, 1994. 33(23): p. 7033-40. https://doi.org/10.1021/bi00189a009
70. Minuzzo, M., et al., Interference of transcriptional activation by the antineoplastic drug ecteinascidin-743. Proc Natl Acad Sci U S A, 2000. 97(12): p. 6780-4. https://doi.org/10.1073/pnas.110154297
71. Welch, J.J., F.J. Rauscher, 3rd, and T.A. Beerman, Targeting DNA-binding drugs to sequence-specific transcription factor. DNA complexes. Differential effects of intercalating and minor groove binding drugs. J Biol Chem, 1994. 269(49): p. 31051-8.
72. Melnikova, A.F., et al., Accessibility of the minor groove of DNA in chromatin to the binding of antibiotics netropsin and distamycin A. Mol Biol Rep, 1975. 2(2): p. 135-42.
73. Wang, S., et al., Minor groove to major groove, an unusual DNA sequence-dependent change in bend directionality by a distamycin dimer. Biochemistry, 2011. 50(35): p. 7674-83. https://doi.org/10.1021/bi200868r
74. Vorländer, M.K., et al., Molecular mechanism of promoter opening by RNA polymerase III. Nature, 2018. 553(7688): p. 295-300. https://doi.org/10.1038/nature25042
75. Abascal-Palacios, G., et al., Structural basis of RNA polymerase III transcription initiation. Nature, 2018. 553(7688): p. 301-306. https://doi.org/10.1038/nature25129