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CLINICAL MEDICINE & PHARMACOLOGY

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Contents

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CMP

Research article

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Effects and Implementation Pathway of a High-Protein Diet Combined with Exercise Intervention in Adolescent Obesity

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Abstract: With the continuous improvement in living standards, the incidence of adolescent obesity has shown an increasing trend. Adolescent obesity not only affects growth, development, and mental health but also increases the risk of future chronic diseases. Existing intervention methods primarily include exercise, dietary modification, and pharmacotherapy, each with inherent limitations. Research suggests that a combined exercise and nutritional strategy can effectively improve body composition and overcome the negative effects of single-modality interventions. Therefore, this paper aims to provide a narrative review of the mechanisms and implementation pathways of a high-protein diet combined with exercise intervention in adolescent obesity, to enhance understanding of its effects on adolescents' physical and mental health, and to offer a reference for theoretical development and clinical practice in related fields.

Keywords: Adolescent obesity; High-protein diet; Exercise intervention

Introduction

Current status of adolescent obesity

Adolescent obesity has become a major global public health challenge. According to the MSD Manuals 2024 Global Report, approximately one-fifth of children and adolescents worldwide are overweight or obese. Data from 2022 also indicate a rapidly increasing prevalence of obesity among children and adolescents in China. [1] Obesity adversely affects mental health, motor skills, and social integration, and it significantly increases the risk of developing metabolic diseases such as type 2 diabetes, hypertension, and non-alcoholic fatty liver disease in adulthood. [2] Unlike adults, adolescents are in a critical phase of growth and development, with unique energy and nutrient requirements. [3] Therefore, any obesity treatment plan for this population must aim to reduce body fat while simultaneously ensuring normal growth, sexual development, and healthy brain development.

Limitations of existing intervention models

Dietary intervention alone

Dietary intervention alone, typically a low-calorie balanced diet, can induce short-term weight loss but is often followed by a significant loss of lean body mass (LBM). LBM is a primary determinant of resting metabolic rate (RMR); its reduction lowers RMR, thereby increasing the likelihood of weight regain. This creates a detrimental cycle of "weight loss → metabolic decline → weight regain." [4] Furthermore, very low-calorie diets may lead to insufficient nutrient intake, compromising adolescent growth and development. Such restrictive diets are also difficult to sustain long-term, increasing the risk of weight rebound. [5]

Exercise intervention alone

When exercise is not accompanied by dietary adjustments, the energy deficit created can be easily offset by increased food intake, resulting in minimal fat loss. [6] Moreover, if the exercise regimen consists primarily of aerobic activities without resistance training, it is challenging to stimulate muscle protein synthesis under a negative energy balance. The consequent loss of muscle mass, coupled with a reduced metabolic rate, is also detrimental to long-term weight management. [7]

Value of combined intervention

Given these limitations, a combination of a high-protein diet and exercise—particularly when resistance training is

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included—has emerged as a promising strategy for adolescent obesity. Adequate protein intake provides the essential amino acids for muscle repair and growth following exercise, while also promoting satiety, which improves dietary adherence. [8] Regular exercise, especially resistance training, directly stimulates muscle protein synthesis and increases total energy expenditure. This combined approach shifts the goal from mere "weight loss" to "improving body composition"—reducing fat mass while preserving or even increasing LBM, thereby enhancing metabolic health. [9] This study is designed as a narrative review to systematically (though not exhaustively) synthesize the proposed mechanisms and practical effects of a high-protein diet combined with exercise on adolescent obesity, and to propose a scientific implementation pathway, offering a reference for both theory and clinical practice.

Definition of Core Concepts

Adolescent obesity

Adolescent obesity is defined as a chronic metabolic state in individuals aged 10–19 years, characterized by excessive body fat accumulation that impairs current or future health. Diagnosis is primarily based on the Chinese standard, "Screening for Overweight and Obesity in School-Age Children and Adolescents," which uses age- and sex-specific body mass index (BMI) percentiles. Obesity is typically defined as a BMI at or above the 95th percentile for the corresponding age and sex. [10] Waist circumference and waist-to-height ratio are also recommended as adjunctive measures to assess abdominal obesity and associated metabolic risks. [11]

High-protein diet

A high-protein diet is a dietary pattern in which the proportion of energy derived from protein is increased to 20%–30% of total daily caloric intake (compared to 10%–15% in a normal balanced diet), or protein intake reaches 1.5–2.0 g per kilogram of body weight per day. [12] In practice, this is often calculated based on ideal body weight or fat-free mass to avoid overestimation in individuals with high body fat. The total energy intake is maintained at an appropriate level, and the overall diet remains balanced. The core principle is to select high-quality, low-fat protein sources, such as lean meats, poultry, fish, eggs, low-fat or skim dairy products, and soy products, integrating these within a holistic healthy eating pattern rather than simply increasing protein intake. [13]

Exercise intervention

In this paper, exercise intervention refers to a planned, structured, and purposeful physical activity program based on exercise science, aimed at improving body composition and metabolic health in obese adolescents. It is primarily divided into two types: aerobic exercise and resistance training. A comprehensive and effective exercise program typically integrates both modalities and clearly prescribes the frequency, intensity, time, and type (FITT principle). For adolescent obesity, the program must be carefully tailored to the physiological characteristics of their developmental stage, as well as individual interests and adherence levels. [14]

Mechanisms of Intervention

Effects on body composition

The combined intervention facilitates fat loss while preserving or increasing muscle mass. Caloric restriction alone often leads to LBM loss, reducing RMR and increasing the risk of weight regain. In the combined approach, regular exercise provides mechanical loading, directly activating muscle protein synthesis pathways. Concurrently, adequate high-quality protein intake supplies the necessary amino acid precursors, effectively counteracting muscle breakdown under a negative energy balance. This establishes an efficient "stimulation + supply" cycle, enabling the body to utilize fat for energy while preserving metabolically active muscle tissue. The result is a lower body fat percentage and increased or maintained fat-free mass, thereby breaking the detrimental cycle of weight loss, metabolic slowdown, and weight regain.

Improvement of metabolic profile

Following the improvement in body composition, the combined approach addresses obesity-related metabolic disturbances through multiple pathways. The preservation or increase of muscle mass significantly enhances insulin sensitivity and glycemic control. [16] The reduction in body fat, particularly visceral adipose tissue, directly lowers the levels of pro-inflammatory adipokines, improves the lipid profile, and reduces triglycerides and low-density lipoprotein cholesterol. [17] Additionally, a high-protein diet can modulate appetite-regulating hormones, increasing levels of satiety hormones (e.g., peptide YY, GLP-1) and decreasing the hunger hormone ghrelin. This appetite-regulating effect, combined with the increased energy expenditure from exercise, facilitates the establishment of a stable and sustainable energy balance. [8]

Effects on exercise performance and physiological metabolism

The combined intervention creates a positive feedback loop that enhances exercise performance and physiological metabolism. Adequate protein supports muscle energy metabolism during exercise and facilitates the timely repair of muscle fibers afterward, which helps delay fatigue, increase muscle strength and endurance, and accelerate post-exercise recovery. [18] Weight loss and improved muscle function reduce the cardiovascular load during daily activities and exercise, alleviate joint stress, and make physical activity feel less strenuous. Aerobic exercise directly improves cardiorespiratory fitness. These physical improvements act

as positive feedback, further motivating adolescents to adhere to the intervention program. [19]

Psychological and behavioral effects

The benefits of the combined intervention extend to psychological and behavioral domains. Achieving tangible changes in body shape, physical fitness, and health markers through personal effort can significantly improve obese adolescents' self-efficacy, body image, and self-esteem, helping to alleviate negative emotions such as anxiety and low self-worth associated with obesity. [20] When a scientific diet and regular exercise together produce positive personal experiences—such as increased energy and a feeling of lightness—this healthy behavior pattern is more likely to be internalized as a personal habit. The resulting improvement in overall physical and mental health, combined with a sense of control over weight management, reinforces the intrinsic motivation for long-term healthy behaviors, which is crucial for the sustainability of obesity intervention effects.

Existing Controversies Regarding Combined Intervention

Despite the promise of a high-protein diet combined with exercise for adolescent obesity, its long-term safety and potential risks—particularly the effects of a high-protein diet on adolescents in a critical developmental stage—remain topics of debate. These controversies primarily focus on the metabolic load on organs, the maintenance of a balanced diet, and the potential for interfering with growth and development.

Organ burden

A primary concern is the increased metabolic load a high-protein diet may place on the liver and kidneys of adolescents. The breakdown of protein produces nitrogenous wastes, such as urea and uric acid, which are primarily excreted by the kidneys. In theory, chronically consuming protein significantly above the recommended intake could increase the glomerular filtration rate and workload on the kidneys, particularly in adolescents whose renal function is not yet fully mature or who have underlying renal conditions. While short-term studies in healthy individuals generally suggest that moderate high-protein intake does not impair renal function, [21] there is insufficient long-term evidence, especially in obese adolescents who may already have subclinical metabolic issues. Furthermore, a high protein load may also increase the liver's gluconeogenic and detoxification workload. Therefore, in practice, it is crucial to screen for pre-existing renal conditions, conduct regular monitoring of renal function, and ensure adequate hydration. [22]

Nutritional imbalance

An overemphasis on high protein can inadvertently lead to an imbalanced diet and deficiencies in other essential nutrients. If adolescents and their families focus excessively on "high protein," they may neglect vegetables, fruits, and whole grains, which are rich in dietary fiber, vitamins, and minerals. This can lead to insufficient intake of these vital nutrients. For example, inadequate fiber intake can impair gut health and satiety, while insufficient calcium, potassium, or magnesium can negatively affect bone health and blood pressure regulation. [23] More concerning, if protein is sourced primarily from poor-quality sources, such as large amounts of red and processed meats, this could also mean excessive intake of saturated fat and cholesterol, which is detrimental to cardiovascular and metabolic health. [24] Therefore, "high protein" must be understood within the context of a balanced diet; the key is to optimize protein quality and quantity, not to overemphasize a single nutrient.

Interference with growth, development, and endocrine function

As adolescents are in a critical period of rapid growth and development, a high-protein diet carries a theoretical risk of interfering with normal hormonal axes and developmental milestones. It has been hypothesized that a long-term low-carbohydrate, high-protein diet could affect the hypothalamic-pituitary-gonadal axis, potentially delaying or altering the normal onset and progression of puberty. [25] However, studies on balanced high-protein diets have not confirmed this, and such concerns are often extrapolated from extreme dietary patterns. [26] Also, a very high protein intake often comes with a significant phosphate load. If calcium intake is insufficient, the calcium-phosphate balance could be disrupted, theoretically posing a long-term risk to achieving peak bone mass. [27] Ensuring adequate calcium and vitamin D intake during the intervention and avoiding extremely low-carbohydrate diets are key strategies to mitigate these risks. It is important to distinguish between these theoretical risks and established findings; the available evidence does not confirm that a well-formulated high-protein diet within recommended ranges harms growth or endocrine function in healthy adolescents.

Implementation Pathway

A practical and safe implementation pathway requires a multi-component, staged approach (**Table 1**).

Conclusion

This narrative review has focused on the proposed mechanisms and scientific implementation pathways of a high-protein diet combined with exercise for adolescent obesity. The available evidence suggests that this combined strategy is a viable approach to improve body composition by reducing fat mass while preserving or increasing lean mass. It may also address metabolic disturbances such as insulin resistance and dyslipidemia, while potentially enhancing exercise performance and psychological well-being. However, the in-

Table 1 | Summary of Implementation Pathway for Combined High-Protein Diet and Exercise Intervention

Component	Key Elements	Details and Considerations
Individualized Assessment	Physical Exam	Height, weight, BMI, waist circumference, body composition (e.g., BIA, DEXA). Blood tests (renal function, lipid profile, glucose, insulin) to rule out secondary obesity and set baselines.
	Dietary Assessment	24-hour diet recalls or food diaries to assess daily energy, macronutrient (especially current protein) and fiber intake, and eating patterns.
	Exercise Capacity	Physical fitness tests or questionnaires to evaluate current activity levels, interests, skills, and sedentary time.
	Psychological Check	Assess motivation for weight loss, self-efficacy, emotional eating, and family support structure.
Intervention Prescription	Dietary Targets	Protein: 1.5–2.0 g/kg of ideal body weight or fat-free mass (not actual weight), or 20-25% of total energy.Distribution: Spread evenly across 3-4 meals, with a focus on post-exercise intake (20-40g).Sources: Prioritize lean meats, poultry, fish, eggs, low-fat dairy, soy, and legumes. Ensure adequate fiber, calcium, and vitamin D.
	Exercise Prescription (FITT)	Aerobic Exercise:- Frequency: 3–5 sessions/week.- Intensity: Moderate (e.g., 40-60% HRR, RPE 12-14).- Time: 30–60 minutes/session.- Type: Walking, jogging, swimming, cycling.Resistance Training:- Frequency: 2–3 non-consecutive sessions/week.- Intensity: 60-80% of 1RM.- Time: 30–45 minutes/session.- Type: Bodyweight exercises, resistance bands, or machine-based exercises for major muscle groups.
Multi-Dimensional Support	Family	Provide education to parents on intervention principles, assist in improving family meals, and offer emotional support.
	School	Integrate resistance training into PE classes. Provide nutrition/health education focusing on protein and exercise. Involve school dietitians for guidance.
	Digital Tools	Use apps for food logging and exercise tracking to facilitate monitoring and feedback. Establish peer support groups for interaction and motivation.
Monitoring & Adjustment	Core Indicators	Re-assess body composition, anthropometrics, and blood markers at regular intervals (e.g., monthly, quarterly). Review diet and exercise logs for adherence.
	Safety Checks	Monitor renal function (creatinine, BUN), hydration, and any gastrointestinal discomfort. Watch for signs of nutrient deficiencies.
	Feedback Loop	Professionals review monitoring data with the adolescent and family, translating positive changes into reinforcement. Adjust the plan based on progress (e.g., fine-tune protein intake, modify exercise intensity, or set new behavior goals).

tervention must be carefully implemented to mitigate the theoretical risks of a high-protein intake on renal function and nutritional balance in adolescents. Future research should prioritize long-term follow-up studies with rigorous safety monitoring, individualized assessments, and the development of collaborative support systems involving families, schools, and communities to ensure the safety, efficacy, and sustainability of this combined intervention. It is crucial to emphasize that "high-protein" should always be understood within the context of a balanced diet tailored to the individual needs of the growing adolescent.

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Review article

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

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

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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.

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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?

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Call for Papers

Scope

CMP particularly values clinician-led studies, practice-based evidence from primary care institutions, and collaborative contributions that translate emerging medical knowledge into improved patient outcomes. Our areas of interest include, but are not limited to:

Clinical Medicine and Specialties

- Precision oncology and individualized treatment strategies;
- Chronic disease management and multi-morbidity care;
- Rare diseases and therapeutics for special populations;
- Real-world studies and multicenter clinical practice analyses.

Pharmacology and Pharmaceutical Sciences

- Clinical evaluation of new and repurposed drugs;
- Pharmacokinetics, pharmacodynamics, and drug interaction research;
- Medication safety, pharmacovigilance, and adverse event monitoring;
- Interdisciplinary studies in oncology pharmacology, chronic medication regimens, and AI-assisted drug development.

Public and Global Health

- Evidence-based approaches to communicable and non-communicable diseases;
- Implementation research on clinical policies and treatment accessibility;
- Regional analyses of healthcare innovation and outcome disparities.

Biomedical Sciences and Emerging Technologies

- Applications of AI, big data, and machine learning in pharmacological analysis;
- Innovations in clinical diagnostics, precision medicine, and molecular testing;
- Translational research in imaging, regenerative medicine, and therapeutic devices.

Healthcare Systems and Practice

- Clinical decision support systems and electronic health record integration;
- Practice-based improvements in patient safety and treatment adherence;
- Models for managing chronic illness in complex healthcare settings.

Ethical and Social Considerations

- Ethical conduct of clinical trials, patient autonomy, and informed consent;
- Social, cultural, and economic influences on clinical decision-making and patient care.

Special Areas of Focus

- Geriatric medicine and aging-related care models;
- Sports medicine, rehabilitation, and preventive strategies;
- Antimicrobial resistance and innovations in infection control.

Methodological Innovations

- Real-world clinical research design and drug re-evaluation frameworks;
- Systematic reviews, meta-analyses, and evidence synthesis strategies;
- Feasible tools for use in primary care and low-resource settings.

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Review Articles (4,000–8,000 words): Critical overviews and syntheses of literature in clinical medicine and pharmacology.

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