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Molecular Mechanisms and the Latest Advances in Precision Therapies for Spinal Muscular Atrophy

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Abstract. Spinal Muscular Atrophy (SMA) is a serious autosomal recessive neuromuscular disorder. In the past few years, the rapid progresses of molecular genetics and precision medicine have greatly pushed the understanding of disease cause and the making of treatment methods for SMA. This review systematically sums up the newest advances in molecular mechanisms and accurate therapies of SMA during the time from 2024 to 2026. It highlights the regulatory roles of *SMN1/SMN2* genes, non-coding RNAs, and epigenetic modifications, as well as pathophysiological alterations and disease-modifying factors induced by SMN protein deficiency. Furthermore, the clinic significances of *SMN* gene examination, biology markers, imaging examination, and newborn screening are all narrated in this paper. The effect and security of many accurate treatment methods, including antisense oligonucleotides, AAV-mediated gene substitution, small-molecule splicing modulators, and gene editing, are also assessed. At present, the problems that exist include the off-target effects brought by gene editing, relatively expensive treatment expenses, restricted acquisition channels, and not enough long-term follow-up observation data. Future directions include optimization of technical strategies, combination therapy, and translational application of biomarkers.

Keywords: Spinal Muscular Atrophy, SMN1 Gene, SMN2 Splicing Regulation, Gene Therapy, Antisense Oligonucleotide

1. Introduction

Spinal Muscular Atrophy (SMA) is a destroying heredity neuromuscular disorders that is featured by the continuing losing of spinal front angle motor nerve cells, therefore it brings about symmetric muscle power lack and withering. In clinical classification, SMA is divided into four subtypes (I–IV) according to onset age and highest motor ability, and the disease exhibits prominent phenotypic heterogeneity with marked differences among these subtypes. Type I is the most serious one, and therefore it often causes death in infancy when no treatment is given, by contrast type IV appears in grown-up people and has a relatively gentle developing process [1]. As a top genetic reason for baby death, SMA puts a heavy world load on patients, family members and medical care systems.

The ten years that just passed have witnessed a model change in the handling of SMA, which is pushed forward by progress in molecule heredity study and accurate medical treatment [2]. The finding that Survival Motor Neuron 2 (*SMN2*), a nearly same duplicate gene of Survival Motor

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Neuron 1 (*SMN1*), is able to partially make up for *SMN1* lack by means of alternative splicing has built the base for all presently approved disease-modifying treatment methods. Antisense oligonucleotides (ASOs), AAV-mediated gene substitution and small-molecule splicing regulators have been proven to have notable effect in changing the natural course of SMA. However, the majority of past summary literatures concentrate on studies which were issued before 2024, hence, leaving an important gap in the comprehension of the newest advances in this quickly changing domain.

This review provides a comprehensive and up-to-date summary of SMA research from 2024 to 2026. It systematically analyzes breakthroughs in molecular pathogenesis. These include new SMN gene regulation mechanisms and disease-modifying factors found by multi-omics. It also discusses advances in clinical diagnosis, such as optimized genetic testing, novel biomarkers, and expanded global newborn screening programs. The review highlights the latest therapeutic advances. These include high-dose ASO regimens, long-term gene therapy results, and preclinical gene editing progress. Finally, it addresses current challenges and future directions, supports clinical decision-making, and identifies key research priorities.

2. Molecular pathogenesis of SMA

2.1. Genetic basis and regulatory mechanisms

SMA results from the homozygous deletions or pathogenic mutations that happen in the *SMN1* gene which locates on chromosome 5q13.2. The most frequently seen gene change is two same allele deletion of exon 7 (about 95 percent of all cases), thus the rest cases are caused by point mutations, small insertion or small deletion. SMN protein is ubiquitously expressed in all tissues and plays indispensable roles in spliceosome assembly, pre-mRNA splicing, axonal transport, and synaptic function. Its lack gives priority to influencing spinal motor neurons, which brings about gradual degeneration and the following muscle wasting.

Human beings have a nearly same paralog, *SMN2*, which has difference from *SMN1* by only one C-to-T change at the 6 position of exon 7. This alteration breaks an exonic splicing intensifier and produces a repressor, therefore leading to exon 7 being skipped in around 90% of SMN2 transcription products. The finally obtained truncated SMNΔ7 protein has no stability and is quickly broken down, therefore it only generates 10–15% of the functional complete-length SMN protein. The copy number of *SMN2* is the main factor that changes the severity of SMA, hence higher copy numbers have connection with lighter disease forms. Recent research works have discovered new cis-acting control components inside *SMN2* intron 6 and 7 which adjust exon 7 inclusion, hence giving new treatment targets. In addition, RNA-binding proteins, including hnRNPs and SR proteins, exert tissue-specific regulatory effects on *SMN2* splicing.

Non-coding RNAs (ncRNAs) have already come forth as key regulators for the expression of *SMN* gene. MicroRNA (miR) molecules like miR-9, miR-124 and miR-183 make direct targeting on *SMN* mRNA, therefore promote its degradation or inhibit the translation process. On the opposite side, if one suppresses these miRNAs in cell and animal SMA models, it can bring about the increase of SMN protein level, and hence improve the neuron-related appearance features. Long non-coding RNAs regulate *SMN2* splicing by acting as molecular sponges for splicing factors or recruiting chromatin modifiers to the *SMN* locus. Epigenetic modifications, which include DNA methylation and histone acetylation, also have influence on *SMN* expression. In recent times, the whole-genome methylation researches have found the differently methylated areas in the *SMN*

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promoter and enhancer, these areas are related to disease severity, therefore they suggest that epigenetic therapies can become a hopeful additional method for current treatments [3].

2.2. Pathophysiology and disease modifiers

The lack of *SMN* breaks many cellular processes in movement nerve cells, therefore it brings about function abnormality and death. It leads to problems in axonal transportation, damage to presynaptic vesicle cyclic utilization and neurotransmitter release at neuromuscular junctions (NMJs), hence resulting in NMJs unstability and denervation. In recent times, many investigations have pointed out that extensive splicing wrong cases in motor neurons, specially in genes which take part in neuronal growth and function, are one important pathopoiesis mechanism.

Although *SMN1* loss is the primary cause of SMA, marked phenotypic variability exists even among patients with the same *SMN2* copy number, indicating the presence of additional disease modifiers. Multi-omics methods have played the instrument role in the finding of these modifiers [4]. In recent days, studies of whole genome association have found genetic variations outside the *SMN* locus which can affect the severity, including those which take part in muscle growth, inflammation and nerve cell survival.

Myostatin, which is a negative adjusting factor for muscle bulk, has become a key peripheral disease influencing factor. Its expression is significantly upregulated in SMA muscle tissue, and inhibition of myostatin signaling in animal models increases muscle mass, improves strength, and enhances motor function—even without increasing *SMN* levels [5]. These research results have thus led to clinical tests of myostatin suppressors as auxiliary treatment methods. Epigenetic changes, which contain different DNA methylation and histone changes, also make contribution to phenotype difference and are potential treatment targets.

3. Clinical diagnosis and newborn screening of SMA

3.1. Clinical manifestations and classification

SMA presents with a wide spectrum of phenotypic manifestations. Type I SMA, which is named Werdnig-Hoffmann disease, has its onset occur before the age of 6 months. Affected infants cannot sit independently, display severe hypotonia, and develop progressive respiratory and swallowing failure; most die before age 2 years without treatment.

Type II SMA (Dubowitz disease) has an onset between 6 and 18 months of age. Patients are able to sit but at no time can they walk by themselves, they grow gradual weakness, spinal curvature and respiratory problem, though the majority of them live to adult age with the help of supportive treatments.

Type III SMA (Kugelberg-Welander disease) has its onset after 18 months, therefore most patients can reach the ability of walking independently. The disease progresses slowly, leading to proximal muscle weakness, difficulty climbing stairs, and frequent falls; numerous people lose the walking capability when they are in the adult stage.

Type IV SMA, the most gentle type, manifests after the age of 30 years, and it shows slowly developing weakness of near-end lower limbs. Respiratory and bulbar involvement is uncommon, and life expectancy remains normal.

SMA that occurs after adulthood is still a problem for diagnosis, therefore it is often wrongly diagnosed as limb-girdle muscular dystrophy, amyotrophic lateral sclerosis or chronic inflammatory demyelinating polyneuropathy. Slow developing course, gentle clinical signs and absence of family

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medical history therefore lead to diagnostic delays. Key diagnostic clues include symmetric proximal muscle weakness, preserved deep tendon reflexes, absence of sensory symptoms, and subtle childhood motor abnormalities on history taking.

Respiratory and skeleton complications are main reasons of sickness and death. Weakness of the respiratory muscles leads to hypoventilation during the night, repeated infections and chronic respiratory failure. Skeletal complications contain progressive scoliosis (in majority of type II/III patients) and joint contractures, which greatly bring influence to life quality and need multidisciplinary handling.

3.2. Diagnostic technologies and biomarkers

The diagnosis of SMA is confirmed through the genetic examination which looks for deletions or mutations of the *SMN1* gene. The traditional assays which are based on PCR, together with Sanger sequencing, possess limitations when they are used for detecting complex rearrangements and for carrying out accurate quantification of *SMN2* copy number. Recent advances have enabled more comprehensive detection methods. Digital PCR has emerged as the gold standard for *SMN1/SMN2* copy number analysis, and long-read sequencing allows the identification of previously undetectable complex structural variants within the *SMN* locus [6].

Multi-omics research works have found out hopeful biomarkers for early diagnose, illness watching and treatment reaction evaluation. The levels of SMN protein that circulate in blood and cerebrospinal fluid (CSF) have correlation with the severity of disease and the response of treatment [7]. Exosomes that are produced by neurons, which contain SMN protein and special miRNAs, give a method that is non-invasive for measuring the *SMN* levels in neurons. Metabolomic studies have revealed alterations in lipid, amino acid, and energy metabolism, indicating that numerous metabolites hold diagnostic and prognostic potential..

Imaging methods have a significant function in diagnosis and monitoring. Muscle MRI gives measurement to fat infiltration and volume changes, therefore it provides objective targets for disease progression. Electromyography and nerve conduction investigation items can separate SMA from other neuromuscular diseases and evaluate the degree of denervation. Recent advances in ultrasound technology allow non-invasive assessment of muscle structure and NMJs function, serving as a promising alternative to electromyography for long-term clinical monitoring.

3.3. Newborn screening programs

Newborn check for SMA has appeared as a key public health project, allowing early diagnosis and handling before symptom beginning. The effective therapies which can change the properties of disease, and the quick, money-saving gene examinations, therefore have speeded up the whole world's newborn screening (NBS) putting into practice. By 2026, over 50 countries have implemented or planned to launch SMA NBS, covering approximately 40% of newborns worldwide.

Population-based NBS programs in the United States (US) and Europe have demonstrated that presymptomatic identification and prompt treatment yield significantly better outcomes compared with clinical diagnosis. Infants who get treatment before symptoms appear reach movement development marks that are almost not different from healthy children, hence most of them grow to walk on their own and have normal breath work.

In the domain of SMA NBS, China has already obtained great advancement. Quite a few provinces (e. g., Beijing, Shanghai, Guangdong) all have already started pilot projects, and the whole country will carry out implementation in 2028. Preparatory data indicate NBS can obviously

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cut down the time that is delayed in diagnosis, therefore it lets the starting of early treatment be achieved. Nevertheless, several challenges remain, including screening costs, standardized testing protocols, and guaranteed access to treatment for screen-positive infants. Integrated systems that combine screening, diagnosis, treatment and follow-up are necessary for maximizing the benefits of NBS.

4. Precision therapeutic strategies for SMA

4.1. Approved and optimized disease-modifying therapies

At present, three therapies that can change the course of disease have got approval for SMA: nusinersen (ASO), onasemnogene abeparvovec (AAV9 gene replacement) and risdiplam (small-molecule splicing modulator). Recently, clinical experiments and long-time follow-up researches have given key understandings about their best usage.

Nusinersen, which is the first SMA therapy that has got approval, is given through intrathecal injection to make *SMN2* exon 7 inclusion have increasing. The DEVOTE clinical test has made comparison between high-dose (50 mg loading dose, 28 mg maintenance dose) and standard-dose nusinersen among patients with type I/II SMA. High-dose nusinersen yields significantly greater improvements in motor function, particularly in infants treated before six months of age, while maintaining a safety profile comparable to the standard dose [8]. These result have caused the wide use of high-dose treatment plans for serious infantile SMA.

Onasemnogene abeparvovec is a one-time intravenous AAV9-carried gene substitute treatment that brings a working *SMN1* transgene. The 64-week STEER research has carried out evaluation on intrathecal onasemnogene abeparvovec among type I SMA infant patients, thus it has proved that sustainable promotions exist in motor ability, breath function and living duration, hence most patients have reached targets which were not seen in natural disease process [9]. However, the treatment effect changes according to the treatment age and the basic movement function before treatment. Recent progress in vector engineering focuses on reducing immunogenicity, enhancing CNS tropism and expanding packaging capacity, with novel capsids currently under preclinical and early clinical development.

Risdiplam is a take-by-mouth small molecular shearing regulator which raises *SMN2* exon 7 hold in both central nerve system and surround organization. Recent long-time prolongation researches have shown that lasting enhancements of motor function and survival rate exist in all SMA type patients. It possesses a good safety situation, with frequently seen bad effects including upper breathing channel infections, loose bowels and headache. Risdiplam is particularly valuable for patients ineligible for intrathecal injection or gene therapy, as well as adults with milder disease phenotypes [10].

4.2. Emerging therapeutic strategies

Gene editing is the next treatment boundary, it can provide possible permanent healing through fixing the basic gene problem. Base and prime editing have particularly big hope, which can let accurate *SMN2* splicing correction happen and do not need double-strand DNA breaks. Recent preclinical animal studies have demonstrated that base editing of the *SMN2* C6T variant in exon 7 results in high levels of full-length SMN protein, as well as significant improvements in motor function and survival in SMA mouse models. Prime editing likewise has manifested achievement in rectifying *SMN*1 point mutations in patient-originated iPSCs and animal models [11]. But, problems

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still exist in the optimization of CNS conveyance, the lessening of off-target effects and the handling of immune reactions toward editing devices.

Combined treatment methods that aim at multiple disease-causing paths are now being vigorously studied. The combination of SMN-upregulating agents and myostatin inhibitors has shown great promise in preclinical studies, as it simultaneously enhances motor neuron survival and muscle growth, yielding greater functional benefits than monotherapy. Quite a number of clinical experiments are now carrying out evaluation on the safety and effect degree of combining risdiplam or nusinersen together with myostatin inhibitors. Other combination methods include neuro-protective matters, anti-inflammation medicines and mitochondrial function promotion agents.

4.3. Comparative analysis of therapeutic options

The availability of multiple therapies has created a need for evidence-based treatment selection. A 2025 network meta-analysis has made a comparison among the three approved treatments for type I SMA, and thus it finds all significantly enhance survival rate and motion function when compared with natural disease course, hence onasemnogene abeparvovec displays the biggest effect in total survival and goal reaching. However, treatment selection must be individualized based on age, disease severity, *SMN2* copy number, and patient preferences.

Nusinersen needs intrathecal injections (four loading doses within two months, then every three months for maintenance), it gets approval for all age groups and all *SMN2* copy counts, and it displays high effect strength on type I SMA and medium effect strength on adult patients. Key safety worried points include reactions related to injection and increased pressure inside the skull, with yearly costs of ~ 750,000(thefirstyear)and 375,000 after that time.

Onasemnogene abeparvovec is administered as a single intravenous infusion and is approved for children under 2 years of age with 1–4 *SMN2* copies. It possesses extremely high effectiveness in type I SMA, particularly when it is given before symptoms appear, but it bears risks of liver poison damage, low platelet count and immune reactions, with a single cost of ~$2.1 million.

Risdiplam is be taken by mouth one time every day, it has been approved for every age group and all *SMN2* copy quantity values. It possesses high curative effect on type I SMA and medium effect in grown-up people, therefore it has the most favorable safety characteristics. Common bad reactions are stomach bowel discomforts and nose throat infections, with one year cost of ~$340,000.

For presymptomatic or early-onset type I SMA infants, onasemnogene abeparvovec is recommended as first-line therapy due to single-dose administration and superior efficacy. For the patients that are not suitable to receive gene therapy (e. g., already existing AAV antibodies, liver function abnormity), high dosage nusinersen or risdiplam are suitable replacement options. To the older children and adults who have the lighter disease, risdiplam is often chosen by people because it can be taken through mouth and has the good safety. For the condition of rapidly progressive disease or the incomplete response to monotherapy, combination therapy can be considered by clinicians.

5. Safety, challenges and future perspectives

5.1. Safety and prognosis of current therapies

Although the already approved treatment methods have shown very notable effect, they still have problems that cannot be ignored in the aspect of safety. Nusinersen is generally well tolerated, with

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common adverse events including headache, back pain, and post-lumbar puncture syndrome; rare occurrence that has serious consequences include lifted pressure inside skull, sterile meninx inflammation and kidney poisonous injury. Long-term following-up has discovered possible dangers of low blood sodium and blood coagulation problems that need regular checking.

Onasemnogene abeparvovec is associated with serious adverse events, including acute liver failure, thrombocytopenia, and myocarditis. These events typically occur within the first few weeks after infusion and can be managed with corticosteroids and supportive care. Pre-existing neutralizing antibody bodies, they can hinder the effective execution of gene transfer, and hence may bring about an elevation in the risk of adverse events. Long-term follow-up is ongoing to evaluate transgene expression persistence and late-onset adverse events.

Risdiplam possesses the most advantageous safety situation, with frequently occurring slight-to-medium alimentary canal symptoms and upper breath passage infections. No serious treatment-related adverse events have been reported in long-term extension studies, although the effects of long-term administration remain unknown.

Time point of treatment is the most key factor for prognosis, and treatment before symptom coming can have much better results, therefore this is because the motor neuron loss is irreversible. Genetic background, particularly *SMN2* copy number, also strongly influences disease prognosis and treatment response. Rehabilitation and supportive nursing are still very important, early intensive rehabilitation can through maintaining motor ability and preventing complications significantly strengthen the advantages of disease-modifying treatment methods.

5.2. Current challenges and future directions

Although, a large number of studies have obtained very notable progress, many important problems are still existing. Gene editing techniques meet obstacles in transmission efficiency, off-target effects and immune reactions. The high expense of already approved treatment methods still is a main obstacle for people to get treatment, especially in low and middle income countries. Long-term follow-up data have limitation, especially regarding gene therapy, and the persistence of treatment influences through many decades still has not been clarified. Current existing therapies exhibit limited efficacy in elder patients and the persons who have late-stage illness.

The future research work therefore should place emphasis on a number of key domains: optimizing gene editing instruments and deliver systems for promoting effectiveness and security; the developing combination therapies targeting multiple pathogenic pathways; the expanding of global newborn screening projects; carrying out verification work on biological markers for diagnosis, prognosis and treatment condition monitoring; and cutting down treatment expenses to promote the accessibility.

6. Conclusion

The period from 2024 to 2026 has seen unprecedented progress in SMA molecular mechanisms and precision therapy development. Studies have greatly clarified the regulatory mechanisms of the *SMN* gene. These include regulation by non-coding RNAs and epigenetic modifications. New disease-modifying factors have been identified through multi-omics approaches. Optimized genetic testing, novel biomarkers, and expanded newborn screening programs have enabled earlier and more precise clinical diagnosis.

In clinical practice, optimized genetic testing, new biomarkers, and the expanded newborn screening programs have enabled earlier and more accurate diagnosis. In the aspect of treatment,

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high-dose nusinersen treatment plans, long-term effect data of gene therapy and hopeful pre-experiment gene editing outcomes are important milestones. SMA has already completed the transformation from a disease that all people will die of to a condition that can receive treatment. Nevertheless, challenges remain regarding treatment access, long-term safety data, and therapeutic efficacy in older patients.

The combination of molecular mechanism study with newly created treatment technologies is on the fundamental level changing SMA clinical handling. In the future, the research emphasis will move from only raising *SMN* contents to constructing truly personal treatment plans that are matched to every patient's gene background and illness phase. Through continuous research and cooperation, the curative treatment of SMA is within foreseeable reach.

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