JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

Pathophysiological Mechanisms and Clinical Phenotypes of Kennedy Syndrome

Syed Ansar Ahmed*[1], Shaikh Samina Munaf[2]

[1] *Associate Professor, Department of Pharmaceutical Chemistry, Indira College of Pharmacy, Vishnupuri, Nanded, Maharashtra, India*
[2] *Pharmacist, Department of Pharmacy, Government Cancer Hospital, Chhatrapati Sambhajinagar, Maharashtra, India*

Publication history: Received on 10th October 2025; Revised on 26th October 2025; Accepted on 31st October 2025

Article DOI: 10.69613/tckj0088

Abstract: Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy syndrome, is a rare X-linked neuromuscular disorder characterized by the progressive degeneration of lower motor neurons in the brainstem and spinal cord. The disease etiology originates from an unstable CAG trinucleotide repeat expansion within the first exon of the androgen receptor (AR) gene, resulting in an elongated polyglutamine tract. This mutation confers a toxic gain-of-function to the androgen receptor protein, which aggregates within the nucleus of motor neurons and muscles in a ligand-dependent manner, necessitating the presence of circulating androgens for phenotypic expression. Clinical presentation typically manifests in adult males during the fourth or fifth decade of life, encompassing proximal muscle weakness, bulbar palsy, fasciculations, and distinct endocrine disturbances such as gynecomastia and reduced fertility, reflecting a state of mild androgen insensitivity. Recent investigations have shifted the paradigm from a purely neuron-centric view to a broader neuromuscular perspective, implicating skeletal muscle as a primary site of toxicity. Current therapeutic options remain largely supportive, though elucidating the molecular cascades of transcriptional dysregulation, mitochondrial dysfunction, and impaired axonal transport has identified novel targets for disease-modifying interventions. This review discusses about molecular advances with clinical observation to delineate the current state of SBMA research.

Keywords: Spinal and Bulbar Muscular Atrophy; Androgen Receptor; Polyglutamine Disease; Lower Motor Neuron Degeneration; Kennedy Syndrome.

1. Introduction

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy syndrome refers to the spectrum of adult-onset neurodegenerative disorders. It is characterized primarily by the slow, progressive degeneration of lower motor neurons in the anterior horn of the spinal cord and brainstem motor nuclei. Originally delineated in a seminal report by William R. Kennedy and colleagues in 1968, the disorder was identified in 11 males from two families, establishing its inheritance pattern as X-linked recessive [1]. While the defining clinical phenotype is observed almost exclusively in males, female carriers are not entirely spared; they may occasionally manifest subclinical signs such as electromyographic abnormalities or mild cramping, though they rarely develop the full motor syndrome. SBMA holds a significant place in medical genetics as the first identified polyglutamine (polyQ) repeat disease, a class of hereditary disorders that now includes Huntington's disease (HD), dentatorubral-pallidoluysian atrophy (DRPLA), and six forms of spinocerebellar ataxia (SCA). These disorders share a common pathogenic mechanism: the expansion of an unstable CAG trinucleotide repeat within the coding region of the causative gene, leading to the production of proteins containing toxic, expanded polyglutamine tracts.

From an epidemiological perspective, the prevalence of SBMA exhibits notable geographic and ethnic variability. It is estimated to affect approximately 1 in 40,000 males globally, though this is likely an underestimation due to frequent misdiagnosis as Amyotrophic Lateral Sclerosis (ALS) or other motor neuron diseases. Significantly higher prevalence rates have been documented in specific populations, most notably in the Vaasa region of Western Japan and among indigenous populations in Finland, suggesting a founder effect in these communities [2]. In contrast, the condition appears less frequent in African and Caucasian populations of North America and Europe. The identification of these clusters has been instrumental in genetic screening and understanding the population genetics of trinucleotide repeat instability. Despite its relative rarity compared to ALS, SBMA serves as an invaluable paradigm for understanding the molecular underpinnings of neurodegeneration. Its monogenic nature, combined with a well-defined molecular trigger, provides a clearer window into pathogenic mechanisms than sporadic disorders. Uniquely, SBMA pathogenesis is strictly ligand-dependent; the toxicity of the mutant androgen receptor (AR) is precipitated only upon binding with its natural ligands, testosterone or dihydrotestosterone. This feature distinguishes SBMA from other polyQ disorders, where protein

* Corresponding author: Syed Ansar Ahmed

toxicity is often constitutive. Consequently, the disease manifests as a multisystem disorder rather than a pure neuronopathy. It bridges the disciplines of neurology and endocrinology, presenting with a constellation of symptoms that includes not only motor dysfunction but also signs of androgen insensitivity such as gynecomastia, testicular atrophy, and metabolic syndrome [3]. This varying phenotype underscores the systemic toxicity of the mutant protein. Moreover, the ligand-dependency elucidates the profound gender dimorphism observed in SBMA. Female carriers, despite harboring the genetic mutation, are largely protected from neurodegeneration not merely by the presence of a normal X chromosome (X-inactivation), but fundamentally by their significantly lower physiological levels of circulating androgens compared to males. This hormonal protection prevents the nuclear accumulation of the mutant AR, thereby averting the downstream cascade of transcriptional dysregulation and cellular toxicity. Although, contemporary research has expanded the definition of SBMA from a purely motor neuron disease to a primary neuromuscular disease, recognizing that skeletal muscle is not merely a passive victim of denervation but a primary site of mutant AR toxicity

2. Molecular Genetics and Pathogenesis

2.1. The Androgen Receptor Gene Mutation

The molecular basis of SBMA was identified in 1991 as an expansion of a CAG repeat sequence in the first exon of the androgen receptor (*AR*) gene located on the proximal long arm of the X chromosome (Xq11-12) [4]. In the healthy population, the CAG repeat number ranges from approximately 9 to 36. In individuals with SBMA, this repeat tract is expanded, typically ranging from 38 to 62 repeats [5]. There is a recognized inverse correlation between the length of the CAG repeat and the age of onset, as well as a direct correlation with disease severity, a phenomenon known as genetic anticipation, though it is less pronounced in SBMA than in other polyglutamine disorders.

2.2. Ligand-Dependent Nuclear Accumulation

The expansion of the CAG repeats translates into an elongated polyglutamine tract within the N-terminal transactivation domain of the AR protein. The pivotal step in SBMA pathogenesis is the ligand-dependent nuclear translocation of this mutant AR. Upon binding with testosterone or dihydrotestosterone (DHT), the mutant AR undergoes a conformational change, dissociates from heat shock proteins (HSPs) in the cytoplasm, and translocates into the nucleus [6].

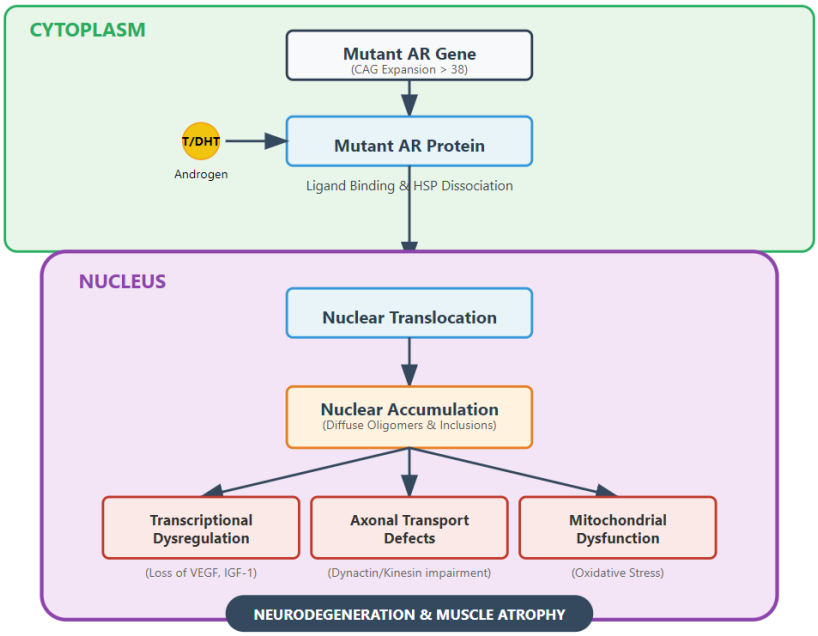

Figure 1. Molecular Pathogenesis of SBMA.

Once intranuclear, the mutant AR fragments tend to oligomerize and form insoluble aggregates or nuclear inclusions (NIs). These inclusions are a pathological hallmark of the disease, found widely in the residual motor neurons of the brainstem and spinal cord, as well as in non-neuronal tissues like the prostate and skin [7]. While early hypotheses suggested these inclusions were the primary source of toxicity, recent evidence proposes that diffuse nuclear accumulation of the mutant protein, rather than the inclusions

themselves, exerts the primary neurotoxic effect. The inclusions may, in fact, represent a protective cellular response attempting to sequester toxic protein species.

2.3. Transcriptional Dysregulation and Axonal Transport

The toxic gain-of-function attributed to the mutant AR involves the disruption of critical cellular processes. A primary mechanism is transcriptional dysregulation. The mutant AR interferes with the function of general transcription factors and coactivators, such as cAMP-response element-binding protein (CBP) and TAFII130, sequestering them into nuclear aggregates and thereby inhibiting the transcription of genes essential for neuronal survival, such as *VEGF* and *IGF-1* [8].

Furthermore, the expansion of the polyglutamine tract affects axonal transport. Efficient transport of organelles and macromolecules is vital for the maintenance of motor neurons, which possess extremely long axons. Studies in murine models indicate that the mutant AR disrupts both anterograde and retrograde axonal transport by inhibiting the function of motor proteins like kinesin and dynein, leading to synaptic dysfunction and eventual dying-back axonopathy [9].

3. Clinical Manifestations

3.1. Neurological Presentation

The clinical onset of SBMA is typically insidious, usually occurring between 30 and 50 years of age. The cardinal neurological feature is slowly progressive muscle weakness and atrophy, predominantly affecting the proximal limb muscles and the bulbar musculature [10]. Patients often report difficulty climbing stairs, rising from a chair, or lifting heavy objects.

Bulbar involvement is a defining characteristic, presenting as dysarthria (slurred speech), dysphagia (difficulty swallowing), and atrophy of the tongue with visible fasciculations. A "quivering chin" or perioral fasciculations are distinct clinical signs highly suggestive of SBMA [11]. Unlike Amyotrophic Lateral Sclerosis (ALS), SBMA purely affects lower motor neurons; therefore, upper motor neuron signs such as spasticity, hyperreflexia, and the Babinski sign are conspicuously absent. Deep tendon reflexes are generally diminished or absent.

Tremor is another frequent early symptom, often postural in nature, which may precede muscle weakness by several years. Muscle cramps are also common and can be a significant source of morbidity. Sensory involvement, while often subclinical, can be detected via electrophysiological studies, manifesting as a sensory neuronopathy primarily affecting dorsal root ganglia [12].

Table 1. Clinical and Pathological Distinctions Between SBMA and ALS

Feature	Spinal and Bulbar Muscular Atrophy (SBMA)	Amyotrophic Lateral Sclerosis (ALS)
Inheritance Pattern	X-linked recessive (affecting males)	Mostly sporadic; 5-10% familial (AD, AR, X-linked)
Age of Onset	Typically 30–50 years	Typically 55–75 years
Progression	Slowly progressive; normal life expectancy common	Rapidly progressive; fatal within 3-5 years
Upper Motor Neuron Signs	Absent (No spasticity, hyperreflexia, Babinski)	Present (Spasticity, hyperreflexia, Babinski sign)
Sensory Involvement	Present (Sensory neuronopathy, reduced SNAP)	Typically absent (Pure motor)
Endocrine/Systemic Signs	Gynecomastia, testicular atrophy, diabetes	Generally absent
Bulbar Involvement	Prominent perioral fasciculations, tongue atrophy	Dysarthria, dysphagia, tongue atrophy
Creatine Kinase (CK)	Markedly elevated (often >5x upper limit)	Normal or mildly elevated
Pathological Hallmark	Intranuclear inclusions of mutant AR	Cytoplasmic inclusions of TDP-43 (mostly)

3.2. Endocrine and Systemic Features

SBMA is unique among motor neuron diseases due to its widespread systemic involvement, particularly signs of androgen insensitivity. The expanded polyglutamine tract impairs the transcriptional activity of the AR, resulting in a partial loss of receptor function. Consequently, patients frequently exhibit gynecomastia (enlargement of breast tissue), testicular atrophy, and erectile dysfunction [13].

Metabolic dysregulation is also prevalent. Patients with SBMA demonstrate a higher incidence of glucose intolerance, diabetes mellitus, and dyslipidemia compared to age-matched controls. Elevation of serum creatine kinase (CK) levels is almost universal in affected individuals, often appearing years before the onset of frank muscle weakness. This elevation is attributed to both neurogenic muscle atrophy and primary myopathic changes, as recent data suggests direct toxic effects of mutant AR on skeletal muscle mitochondria [14].

Table 2. Systemic and Non-Neurological Manifestations of Kennedy Syndrome

System	Clinical Manifestation	Pathophysiological Basis
Reproductive	Gynecomastia (40-60%)	Mild androgen insensitivity; altered estrogen/androgen ratio
	Testicular Atrophy	Impaired spermatogenesis due to AR dysfunction
	Erectile Dysfunction	Reduced libido and androgen partial loss-of-function
	Reduced Fertility	Oligospermia or azoospermia
Metabolic	Diabetes Mellitus / Insulin Resistance	Mitochondrial dysfunction; altered metabolic homeostasis
	Dyslipidemia	Altered lipid metabolism linked to AR dysfunction
Dermatological	Androgenetic Alopecia	Paradoxical effect (often preserved hair in some reports)
Musculoskeletal	High Creatine Kinase (CK)	Primary myopathy; mitochondrial defects in skeletal muscle
	Muscle Cramps	Hyperexcitability of motor axons

4. Diagnosis

4.1. Biochemical and Electrophysiological Evaluation

The diagnostic journey often begins with the identification of elevated serum CK levels, which can be raised to 2–10 times the upper limit of normal. Liver function tests may also show elevated aminotransferases (AST, ALT) due to muscle breakdown rather than hepatic pathology [15].

Table 3. Correlation of CAG Repeat Length in the *AR* Gene with Clinical Phenotype

CAG Repeat Count	Clinical Status	Phenotypic Characteristics
< 10	Rare Normal Variant	Generally asymptomatic; no known pathology
11 – 35	Normal Range	Healthy population; no disease manifestation
38 – 62	Pathogenic Range (SBMA)	Full clinical expression of SBMA
> 62	Extreme Expansion (Rare)	Severe, early-onset phenotype (Juvenile onset reported)
Inverse Correlation	Repeat Length vs. Onset Age	Longer repeats correlate with earlier age of onset (approx. -0.6 to -0.8 correlation coefficient)

There is a "gray zone" (36-37 repeats) where reduced penetrance or mild phenotypes may theoretically occur, though 38 is the standard diagnostic cutoff.

Electromyography (EMG) and nerve conduction studies (NCS) are essential for characterizing the neuromuscular deficit. EMG typically reveals evidence of chronic partial denervation and reinnervation, characterized by large-amplitude, long-duration motor unit potentials, alongside widespread fasciculations and positive sharp waves. Nerve conduction studies often show reduced compound muscle action potential (CMAP) amplitudes. A distinguishing feature from other motor neuron disorders is the frequent reduction or absence of sensory nerve action potentials (SNAPs), indicating an underlying sensory neuronopathy [16].

4.2. Genetic Testing

The definitive diagnosis of SBMA is established via molecular genetic testing. Polymerase chain reaction (PCR) amplification of the *AR* gene allows for the precise quantification of CAG repeats. A repeat number of 38 or greater confirms the diagnosis. Genetic counseling is imperative for confirmed cases, given the X-linked inheritance pattern. Female relatives may be carriers, and while they generally remain asymptomatic due to X-inactivation and low androgen levels, they have a 50% risk of transmitting the mutated allele to their offspring [17]

5. Treatment and Management

5.1. Current Symptomatic Management

At present, there is no curative treatment for Spinal and Bulbar Muscular Atrophy (SBMA). Management remains primarily supportive, focusing on preserving function and improving quality of life. Rehabilitation plays a crucial role; physical therapy is tailored to maintain range of motion and prevent contractures, although high-intensity exercise is generally cautioned against due to the potential for exacerbating muscle damage in the context of elevated creatine kinase levels [18].

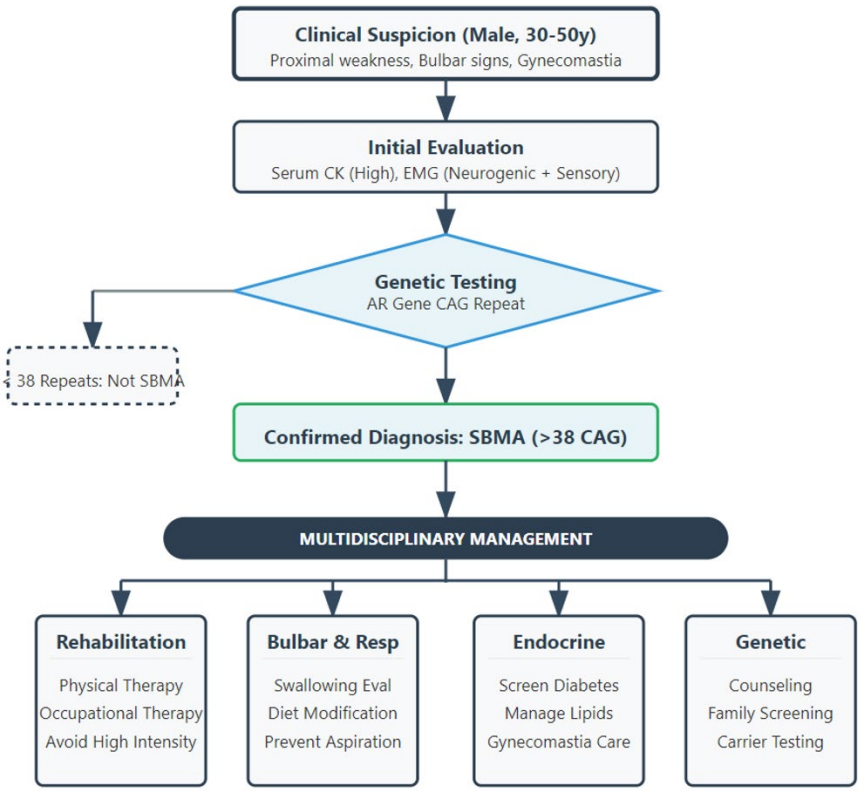

Figure 2. Diagnostic and Management of Kennedy Syndrome

Bulbar dysfunction necessitates proactive management to mitigate the risks of aspiration pneumonia and malnutrition. Speech therapy is utilized to manage dysarthria and dysphagia, while advanced cases may require video-fluoroscopic evaluation to guide dietary modifications. In instances of severe dysphagia, gastrostomy tube placement may be indicated to ensure adequate caloric intake. Respiratory function, though less frequently compromised than in Amyotrophic Lateral Sclerosis (ALS), requires monitoring, particularly in the advanced stages of the disease or during acute infections. Non-invasive positive pressure ventilation (NIPPV) may be beneficial for patients demonstrating nocturnal hypoventilation [19].

5.2. Androgen Deprivation Therapies

Given the central role of ligand-dependent nuclear accumulation of the mutant androgen receptor (AR) in SBMA pathogenesis, androgen deprivation has emerged as the most logical therapeutic target. The rationale posits that reducing circulating testosterone or preventing its binding to the AR should stabilize the mutant protein in the cytoplasm, thereby preventing nuclear aggregation and neurotoxicity.

Leuprorelin, a luteinizing hormone-releasing hormone (LHRH) agonist, suppresses the release of gonadotropins from the pituitary, thereby reducing testicular testosterone production. Initial animal studies demonstrated that leuprorelin treatment significantly rescued motor dysfunction and extended survival in transgenic mouse models of SBMA [20]. However, clinical translation has yielded mixed results. A large-scale, randomized, placebo-controlled phase 2 trial (JASMITT) involving 204 patients suggested that while leuprorelin did not significantly improve swallowing function in the overall cohort, a subgroup analysis indicated potential

benefits in patients with shorter disease duration [21]. This finding suggests that early intervention, prior to irreversible neuronal loss, may be critical for efficacy.

Table 4. Therapeutic Methods and Molecular Targets in SBMA

Therapeutic Strategy	Target Mechanism	Examples	Status
Androgen Deprivation	Reduce ligand-dependent nuclear translocation of mutant AR	Leuprorelin, Goserelin	Clinical Trials (Mixed results)
5α-Reductase Inhibition	Block conversion of T to DHT (reduce AR activation)	Dutasteride, Finasteride	Clinical Trials (No significant motor benefit)
Hsp90 Inhibition	Promote proteasomal degradation of mutant AR	17-AAG (Geldanamycin analog)	Preclinical (Mouse models)
ASC-J9	Dissociate AR from coregulators; enhance degradation	Dimethylcurcumin (ASC-J9)	Preclinical (Promising safety profile)
Gene Silencing	Degrade *AR* mRNA to reduce toxic protein levels	Antisense Oligonucleotides (ASOs)	Preclinical / Early Clinical
Muscle Anabolism	Support muscle hypertrophy; retrograde neuroprotection	Clenbuterol, IGF-1 mimetics	Preclinical / Investigational
Oxidative Stress Reduction	Mitigate mitochondrial dysfunction and ROS	Coenzyme Q10, Vitamin E	Supportive / Adjunct

Another approach involves the use of 5-alpha reductase inhibitors, such as dutasteride, which block the conversion of testosterone to the more potent androgen, dihydrotestosterone (DHT). While this strategy reduces the activation of the AR without fully ablating testosterone levels—potentially preserving muscle mass—clinical trials have yet to demonstrate a statistically significant improvement in motor outcomes, highlighting the complexity of balancing androgen reduction with the anabolic needs of skeletal muscle [22].

Table 5. Randomized Clinical Trials in Spinal and Bulbar Muscular Atrophy

Study (Year)	Intervention	N	Primary Outcome Measure	Findings
Banno et al. (2009)	Leuprorelin (LHRH agonist)	50	Pharyngeal barium swallow residue	Improved swallowing in treated group; reduced nuclear accumulation in biopsy.
Katsuno et al. (2010) (JASMITT)	Leuprorelin	204	Pharyngeal barium swallow residue	No significant difference in overall cohort; subgroup analysis showed benefit in patients with disease duration <10 years.
Fernandez-Rhodes et al. (2011)	Dutasteride (5α-reductase inhibitor)	50	Quantitative Muscle Assessment (QMA)	No significant improvement in muscle strength; secondary outcomes (quality of life) showed no benefit.
Querin et al. (2013)	Clenbuterol (β2-agonist)	16	6-Minute Walk Test (6MWT)	Improvement in 6MWT and FVC observed; well-tolerated. Pilot study.

6. Emerging Therapeutic Targets and Future Directions

6.1. Enhancing Protein Quality Control

The accumulation of misfolded mutant AR proteins places significant stress on the cellular protein quality control machinery. Consequently, upregulating molecular chaperones has been identified as a promising therapeutic avenue. Heat shock protein 90 (Hsp90) stabilizes the mutant AR, facilitating its accumulation. Preclinical studies using Hsp90 inhibitors, such as 17-AAG (17-allylamino-17-demethoxygeldanamycin), have shown that inhibiting Hsp90 induces the degradation of the mutant AR via the proteasome pathway, thereby reducing nuclear inclusions and ameliorating the motor phenotype in mouse models [23].

6.2. Dissociation of Ligand-Receptor Interaction

A novel strategy involves the use of compounds that disrupt the interaction between the AR and its co-regulators without completely suppressing systemic androgen levels. ASC-J9 (dimethylcurcumin), a structural analog of curcumin, has been shown to enhance the degradation of mutant AR by disrupting the AR-Hsp90 complex and preventing AR-coregulator binding [24]. Unlike traditional

anti-androgens, ASC-J9 does not cause significant testicular atrophy or sexual dysfunction in animal models, presenting a more favorable side-effect profile for long-term administration.

6.3. Muscle-Targeted Therapies and IGF-1

The paradigm of SBMA as a purely motor neuron disease has been challenged by evidence suggesting primary skeletal muscle pathology. The overexpression of insulin-like growth factor 1 (IGF-1) in skeletal muscle has been found to counteract muscle atrophy and, remarkably, extend the survival of motor neurons via retrograde signaling [25]. This "muscle-first" hypothesis has spurred interest in anabolic therapies, such as beta-2 adrenergic agonists (e.g., clenbuterol), which have shown promise in improving muscle mass in varying neuromuscular conditions, although cardiac side effects remain a concern.

6.4. Gene Silencing Technologies

The most direct approach to treating SBMA is to suppress the expression of the *AR* gene itself. Antisense oligonucleotides (ASOs) designed to degrade *AR* mRNA have demonstrated high efficacy in suppressing mutant protein levels in both the central nervous system and peripheral tissues of transgenic mice [26]. A key challenge for human application remains the effective delivery of these agents to the spinal cord and muscle tissue, as well as the potential long-term consequences of systemic androgen receptor suppression in adult males.

7. Conclusion

Spinal and Bulbar Muscular Atrophy serves as a paradigm for polyglutamine disorders, illustrating the complex interplay between genetic mutation, hormonal regulation, and selective neuronal vulnerability. The identification of the causative AR gene mutation has facilitated a deep understanding of the disease's molecular pathogenesis, characterizing it as a ligand-dependent toxic gain-of-function disorder. While the clinical phenotype is dominated by lower motor neuron degeneration, the systemic nature of the disease—encompassing endocrine and metabolic dysfunction—mandates a multidisciplinary approach to patient care. Current research underscores a critical therapeutic window in the early stages of the disease and highlights the skeletal muscle as a vital target for intervention, distinct from the motor neuron itself. Although standard androgen deprivation therapies have shown limited success in advanced disease, next-generation strategies focusing on specific degradation of the mutant protein, gene silencing, and neurotrophic support offer cautious optimism. Future clinical trials will likely focus on combinatorial therapies that address both the toxic accumulation of the mutant receptor and the downstream metabolic consequences of neuromuscular failure.

References

[1] Hoffman AS. Hydrogels for biomedical applications. Adv Drug Deliv Rev. 2012;64:18-23.

[2] Lozinsky VI. Cryogels on the basis of natural and synthetic polymers: preparation, properties and application to biotechnology. Russ Chem Rev. 2002;71(6):489-511.

[3] Henderson TM, Ladewig K, Haylock DN, McLean KM, O'Connor AJ. Cryogels for biomedical applications. J Mater Chem B. 2013;1(21):2682-95.

[4] Bencherif SA, Sands RW, Bhatta D, Arany P, Verbeke CS, Edwards DA, Mooney DJ. Injectable preformed scaffolds with shape-memory properties. Proc Natl Acad Sci U S A. 2012;109(48):19590-5.

[5] Cimen D, Ozbek MA, Bereli N, Mattiasson B, Denizli A. Injectable Cryogels in Biomedicine. Gels. 2021;7(2):38.

[6] Rogers ZJ, Bencherif SA. Cryogelation and Cryogels. Gels. 2019;5(4):46.

[7] Lozinsky VI, Galaev IY, Plieva FM, Savina IN, Jungvid H, Mattiasson B. Polymeric cryogels as promising materials of biotechnological interest. Trends Biotechnol. 2003;21(10):445-51.

[8] Shiekh PA, Andrabi SM, Singh A, Majumder S, Kumar A. Designing cryogels through cryostructuring of polymeric matrices for biomedical applications. Eur Polym J. 2021;144:110234.

[9] Plieva FM, Andersson J, Galaev IY, Mattiasson B. Characterization of polyacrylamide cryogels with megapores. J Sep Sci. 2004;27(11):828-36.

[10] Omidian H, Dey Chowdhury S, Babanejad N. Cryogels: Advancing Biomaterials for Transformative Biomedical Applications. Pharmaceutics. 2023;15(7):1836.

[11] Newland B, Eigel D. Cryogels: The value of the cryogelation process for the development of advanced biomedical materials. Biomaterials. 2021;276:121015.

[12] Hassan CM, Peppas NA. Structure and morphology of freeze/thawed PVA hydrogels. Macromolecules. 2000;33(7):2472-9.

[13] Kirsebom H, Mattiasson B. Acrylamide-based cryogels: preparation and application in biotechnology. J Sep Sci. 2011;34(20):2966-74.

[14] Hixon KR, Lu T, Sell SA. A comprehensive review of cryogels and their roles in tissue engineering applications. Acta Biomater. 2017;62:29-41.

[15] Zhao J, Qiu P, Wang Y, Wang Y, Zhou J, Zhang B, et al. Chitosan-based hydrogel wound dressing: From mechanism to applications, a review. Int J Biol Macromol. 2023;244:125250.

[16] Rezaeeyazdi M, Colombani T, Memic A, Bencherif SA. Injectable Hyaluronic Acid-co-Gelatin Cryogels for Tissue-Engineering Applications. Materials. 2018;11(8):1374.

[17] Yue K, Trujillo-de Santiago G, Alvarez MM, Tamayol A, Annabi N, Khademhosseini A. Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. Biomaterials. 2015;73:254-71.

[18] Savina IN, Gun'ko VM, Turov VV, Dainiak M, Phillips GJ, Galaev IY, Mattiasson B. Porous structure and water state in cross-linked polymer and protein cryo-hydrogels. Soft Matter. 2011;7(9):4276-83.

[19] Eggermont LJ, Rogers ZJ, Colombani T, Memic A, Bencherif SA. Injectable cryogels for biomedical applications. Trends Biotechnol. 2020;38(4):418-31.

[20] Villard P, Li M, Smeets NM, Hoare T. Injectable hydrogels for biomedical applications. Adv Healthc Mater. 2019;8(15):1900669.

[21] Zeng B, Qin H, Wang H, Su X, Wang C. Interpenetrating polymer network cryogels with tunable properties and high permeability. Carbohydr Polym. 2021;251:117105.

[22] Savina IN, Zoughaib M, Yergeshov AA. Design and Assessment of Biodegradable Macroporous Cryogels as Advanced Tissue Engineering and Drug Carrying Materials. Gels. 2021;7(3):79.

[23] Priya SG, Gupta A, Jain E, Sarkar A, Dhand C, Kulshreshtha R, Kumar A. Bilayer cryogel wound dressing and scaffold for skin tissue engineering. J Biomater Appl. 2016;31(3):405-19.

[24] Park MJ, An YH, Choi YH, Kim HD, Hwang NS. Enhanced Neovascularization Using Injectable and rhVEGF-Releasing Cryogel Microparticles. Macromol Biosci. 2021;21(11):2100234.

[25] Ali OA, Huebsch N, Cao L, Dranoff G, Mooney DJ. Infection-mimicking materials to program dendritic cells in situ. Nat Mater. 2009;8(2):151-8.

[26] Bencherif SA, Warren Sands R, Ali OA, Li WA, Lewin SA, Braschler TM, et al. Injectable cryogel-based whole-cell cancer vaccines. Nat Commun. 2015;6:7556.

[27] Castanheira EJ, Monteiro LP, Gaspar VM, Correia TR, Rodrigues JM, Mano JF. In-bath 3D printing of anisotropic shape-memory cryogels functionalized with bone-bioactive nanoparticles. ACS Appl Mater Interfaces. 2024;16(15):18386-99.

[28] He T, Li B, Colombani T, Joshi-Navare K, Mehta S, Kisiday J, Bencherif SA, Bajpayee AG. Hyaluronic acid-based shape-memory cryogel scaffolds for focal cartilage defect repair. Tissue Eng Part A. 2021;27(11-12):748-60.

[29] Zhang Y, Wang Y, Chen L, Zheng J, Fan X, Xu X, et al. An injectable antibacterial chitosan-based cryogel with high absorbency and rapid shape recovery for noncompressible hemorrhage and wound healing. Biomaterials. 2022;285:121546.

[30] Raza A, Zhang Y, Hayat U, Liu C, Song JL, Shen N, et al. Injectable zein gel with in situ self-assembly as hemostatic material. Biomater Adv. 2023;145:213225.

[31] Koshy ST, Zhang DK, Grolman JM, Stafford AG, Mooney DJ. Injectable nanocomposite cryogels for versatile protein drug delivery. Acta Biomater. 2018;65:36-43.

[32] Li M, Wei X, You J, Feng J, Liu X, Zhou J, et al. Cryogels with controllable physico-chemical properties as advanced delivery systems for biomedical applications. Mater Today Bio. 2022;14:100259.

[33] Fatoni A, Wijonarko A, Anggraeni MD, Hermawan D, Diastuti H, Zusfahair. Alginate NiFe2O4 nanoparticles cryogel for electrochemical glucose biosensor development. Gels. 2021;7(4):272.

[34] Lu J, Yang X, Xiao J, Wang Y, Yu Y, Wang Y, et al. DNA-functionalized cryogel based colorimetric biosensor for sensitive on-site detection of aflatoxin B1 in food samples. Talanta. 2024;275:126122.