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Transcriptional adaptation opens new therapeutic possibilities for Duchenne muscular dystrophy and rare neuromuscular diseases

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Transcriptional adaptation (TA) has emerged as a powerful form of genetic compensation in which the degradation of mutant mRNA, rather than the loss of protein function, triggers the upregulation of related genes[1,2]. Originally described in zebrafish and *Caenorhabditis elegans* (*C. elegans*)[3,4], and later observed in mammalian cell culture[5], TA was long considered absent or insignificant in human disease. A landmark study by Falcucci *et al.* has now provided the first compelling evidence of TA operating in human cells and in the context of Duchenne muscular dystrophy (DMD), one of the most common and devastating neuromuscular disorders[6].

DMD is an X-linked recessive disease caused by mutations in the *DMD* gene that typically introduce premature termination codons (PTCs), leading to nonsense-mediated mRNA decay (NMD) and near-complete absence of functional dystrophin protein[7,8]. The resulting progressive skeletal muscle degeneration, cardiomyopathy, and respiratory failure culminate in loss of ambulation by adolescence and premature death, often in the third decade of life[9]. Current The Food and Drug Administration (FDA)-approved therapies, including exon-skipping antisense oligonucleotides (ASOs), stop-codon read-through agents such as ataluren, and adeno-associated virus (AAV)-based micro-dystrophin gene therapy (Elevidys), aim to restore some dystrophin function. However, with the exception of micro-dystrophin gene therapy, most remain mutation-specific and are further limited by partial efficacy, immune responses, delivery challenges, and high cost[9-11].

For decades, scientists have observed that utrophin (*UTRN*), the autosomal paralogue of DMD, is naturally upregulated in the sarcolemma of DMD patients and *mdx* mice carrying PTC mutations. This compensatory response was widely

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attributed to the absence of dystrophin protein itself[12]. Falcucci *et al.* elegantly overturned this assumption[6]. Using an inducible system in human HEK293T cells, they introduced a PTC into the alternatively spliced exon 37 of *DMD* via clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) system (CRISPR-Cas9). Pharmacological modulation of transcriptional elongation (via trichostatin A) promoted inclusion of the PTC-containing exon, triggering NMD of mutant *DMD* mRNA and a transcriptionally driven increase in *UTRN* mRNA and utrophin protein (~1.5-2-fold). Critically, blocking NMD with small interfering RNA (siRNA) against UPF1 and SMG6 markedly attenuated *UTRN* upregulation, whereas overexpression of full-length dystrophin did not. Parallel experiments with DMD minigenes carrying PTCs, or even wild-type *DMD* minigenes engineered with self-cleaving hammerhead ribozymes to induce mRNA decay without altering the protein-coding sequence, confirmed that mutant mRNA degradation alone is sufficient to drive TA-mediated *UTRN* upregulation in multiple human cell types, including myotubes[6].

These findings have crucial therapeutic implications. The authors demonstrated that splice-switching ASOs designed to induce out-of-frame exon skipping (and thereby generate PTCs) robustly trigger *UTRN* upregulation. Conversely, when an ASO was used to restore the reading frame in patient-derived $DMD^{\Delta E52}$ myotubes, an approach mirroring approved exon-skipping therapies, *UTRN* upregulation was significantly attenuated. This reveals a previously unrecognized trade-off: while restoring dystrophin is beneficial, it may inadvertently dampen an endogenous compensatory mechanism that has evolved to mitigate disease severity. The study therefore positions TA not merely as a biological curiosity but also as a potentially tunable therapeutic axis. Strategies that deliberately promote limited DMD mRNA decay (e.g., via optimized ASOs, ribozymes, or small molecules) could harness utrophin upregulation while preserving partial dystrophin function, potentially yielding additive or synergistic benefits[6,10].

The broader implications could extend beyond DMD to other rare neuromuscular diseases. Many monogenic disorders are caused by PTC mutations that trigger NMD, and paralogous genes are frequently present in the human genome[13]. The demonstration of TA in human cells opens the door to systematic identification of "adapting genes" across rare disease transcriptomes. Subsequent work has reinforced this view: comprehensive single-cell analyses have revealed widespread paralogue upregulation following gene disruption in diverse mammalian contexts[14], while mechanistic studies show that multiple forms of mRNA decay (not just NMD) can elicit TA[15]. Moreover, TA appears to contribute to genotype-phenotype correlations and genetic robustness, with adapting genes preserving downstream regulatory networks more efficiently than non-adapting ones[16]. Findings by Falcucci *et al.* further provide new perspectives for interpreting clinical variability in inherited disorders[6]. While the reading frame rule predicts that out-of-frame mutations cause severe DMD phenotypes and in-frame mutations result in the milder Becker muscular dystrophy (BMD) phenotype[17], exceptions exist. Likewise, utrophin expression is generally lower in patients carrying in-frame *DMD* mutations[18-22]. Also, relatively increased sarcolemmal utrophin has been reported in some patients with BMD[23], suggesting that additional mechanisms, including potentially TA, may contribute to some exceptional cases.

In the context of DMD, where cardiac involvement is the leading cause of mortality, leveraging TA could confer both skeletal and cardiac benefits. Utrophin can localize to the cardiomyocyte sarcolemma and provide structural support analogous to dystrophin[24]. Complementary research from our group has elucidated key mechanisms of DMD cardiomyopathy, including aberrant Ca^{2+} handling through ryanodine receptor type-2 (RyR2) hyperphosphorylation and oxidation[25,26], connexin-43 remodeling that promotes arrhythmias and fibrosis[27,28], and microtubule dysregulation that exacerbates cytoskeletal instability[28]. These studies highlight that even modest functional compensation at the membrane-cytoskeleton interface, such as that provided by upregulated utrophin, could mitigate the downstream sequelae of dystrophin loss in the

heart. Indeed, preclinical models show that utrophin overexpression ameliorates both skeletal and, to a lesser extent, cardiac pathology[29]. Integrating TA-inducing approaches with existing cardiac-protective strategies (e.g., b-blockers, ACE inhibitors, or microtubule stabilizers) and advanced cardiac monitoring[30] may therefore offer a more holistic therapeutic paradigm for DMD patients.

Nevertheless, important questions remain. The magnitude of *UTRN* induction observed (~1.5-2-fold) is modest, and whether it is sufficient for clinically meaningful benefit in patients, particularly in advanced disease stages, requires further validation *in vivo* and in larger patient cohorts[6,31]. The upstream signaling pathways that link cytosolic RNA decay to nuclear transcriptional activation remain incompletely understood, although emerging data implicate nuclear transport and chromatin regulators[16,32]. It is also unclear why TA is robust for some genes and paralogues but absent for others, and whether off-target or non-paralogous adaptive responses could produce unintended consequences[31]. Recent studies suggest that mutation-specific transcript imbalance may further contribute to variability in dystrophin expression, underscoring the complexity of RNA-based regulatory responses that need to be considered when developing TA-based[33]. Finally, the potential heritability of TA-induced epigenetic states raises the intriguing possibilities for durable, "one-and-done" therapies but also necessitates long-term safety studies[34].

Despite these challenges, the discovery of TA in human DMD represents a paradigm shift. Rather than viewing mutant transcripts solely as substrates for quality-control degradation, we can now recognize them as active signals that mobilize endogenous compensatory programs. For DMD and other rare diseases driven by PTC mutations, this insight reframes therapeutic design: instead of solely replacing or repairing the defective gene product, future strategies could preserve or amplify beneficial mRNA-decay-triggered adaptation. Approaches such as carefully titrated ASOs, engineered ribozymes, or small-molecule modulators of NMD/TA crosstalk could be combined with current exon-skipping, gene-replacement, or CRISPR-based utrophin activation platforms (e.g., recent Genethon CRISPR-Cas9 strategies for sustainable utrophin upregulation)[7]. Such combination therapies may ultimately improve therapeutic efficacy and outcomes both across skeletal and cardiac muscle while potentially reducing dose requirements and immunogenicity, although these possibilities remain to be evaluated in appropriate preclinical and clinical studies.

In summary, Falcucci *et al.* have not only solved a long-standing mechanistic puzzle in DMD but also uncovered a fundamental biological process with broad translational potential[6]. By identifying TA as a promising candidate therapeutic pathway in human diseases, this work lays the foundation for exploring next-generation therapies that work with the genome's own compensatory machinery rather than against it. For patients with DMD and other rare neuromuscular disorders, this perspective offers renewed hope that endogenous resilience mechanisms can be harnessed to slow disease progression and improve quality of life.

DECLARATIONS

Authors' contributions

Conceptualization, writing - original draft: Nusrat A
Writing - review & editing: Wehrens XHT

Availability of data and materials

Not applicable.

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During the preparation of this manuscript, the AI tool GPT-5.6 (version 5.6, released 2026-07-09) was used solely for language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the manuscript. Both authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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