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Perspectives on current models of Friedreich's ataxia

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Friedreich's ataxia (FRDA, OMIM#229300) is the most common hereditary ataxia, resulting from the reduction of frataxin protein levels due to the expansion of GAA repeats in the first intron of the *FXN* gene. Why the triplet repeat expansion causes a decrease in Frataxin protein levels is not entirely known. Generation of effective FRDA disease models is crucial for answering questions regarding the pathophysiology of this disease. There have been considerable efforts to generate *in vitro* and *in vivo* models of FRDA. In this perspective article, we highlight studies conducted using FRDA animal models, patient-derived materials, and particularly induced pluripotent stem cell (iPSC)-derived models. We discuss the current challenges in using FRDA animal models and patient-derived cells. Additionally, we provide a brief overview of how iPSC-based models of FRDA were used to investigate the main pathways involved in disease progression and to screen for potential therapeutic agents for FRDA. The specific focus of this perspective article is to discuss the outlook and the remaining challenges in the context of FRDA iPSC-based models.

KEYWORDS

iPSC (induced pluripotent stem cell), disease model cell, triplet repeat disease, frataxin, ataxia

Introduction

The prevalence of FRDA is 1 in 50,000 people, and the median age of onset is 10–15 years (Indelicato et al., 2020). Wheelchair use is generally necessary for around 15 years, and the average lifespan of FRDA patients is reported to be 36 years (Delatycki and Bidichandani, 2019). Approximately 96% of FRDA patients carry homozygous GAA triplet repeat expansion in the first intron of the frataxin (*FXN*) gene. The remaining 4% carry a heterozygous phenotype for GAA repeats with missense mutations in one allele and an expanded allele in the other (Al-Mahdawi et al., 2018). Normally, there are 5–33 GAA repeats in the first intron of the *FXN* gene; however, FRDA patients may have up to 1300 GAA repeats. Individuals with longer repeats show symptoms earlier and with increased severity (Delatycki et al., 2000; Delatycki and Bidichandani, 2019).

Friedreich's ataxia is an autosomal recessive disorder with neurological and non-neurological manifestations. Neurological symptoms include progressive ataxia of gait and limbs, increased muscle tone, decrease in or loss of position sense and tendon reflexes, difficulty swallowing, and dysarthria (Filla et al., 1990; Parkinson et al., 2013). Additionally, neuroinflammation and upregulation of glial activation in the

TABLE 1 FRDA iPSC-based models and main findings observed.

FRDA iPSC-based models	Main phenotypes observed	References
FRDA iPSC-derived neurons	Delayed development of full electrophysiological functionality, reduced mitochondrial potential	Hick et al. (2013), Codazzi et al. (2016)
	Enhanced cleavage of initiator caspase-9 and effector caspase-3 activation	Igoillo-Esteve et al. (2015)
	Quantitative proteomic analysis of HDAC inhibitor treatment	Shan et al. (2014)
	Promising effects of Syn-TEFs	Erwin et al. (2017)
	Transcriptional profiling of isogenic and FRDA iPSC-derived neurons and investigation of the effect of HDAC inhibitors	Lai et al. (2019)
	Generation of a novel FRDA iPSC-derived neuronal reporter system and screening of compounds using this system	Schreiber et al. (2022)
FRDA iPSC-derived cardiomyocytes	Characteristics of respiration-compromised mitochondria, mitochondrial iron accumulation	Hick et al. (2013)
	Disorganized mitochondrial network, mitochondrial DNA depletion, hypertrophic cardiac stress responses, use of FRDA iPSC-derived cardiomyocytes as a drug screening platform	Lee et al. (2014), Lee et al. (2016)
	Calcium signaling impairment	Crombie et al. (2017)
	Promising effects of Syn-TEFs	Erwin et al. (2017)
	Observation of lipid droplets	J. Li et al. (2019)
	Excision of repeats via zinc finger nucleases and upregulation of *FXN*	J. Li et al. (2019)
	Strong positive correlation between the contractility/developed force and *FXN* expression is observed in FRDA iPSC-derived cardiomyocytes	A. O. T. Wong et al. (2019)
	Hepcidin (HAMP)–ferroportin (FPN) axis impaired in FRDA iPSC-derived cardiomyocytes	Bolotta et al. (2019)
FRDA iPSC-derived endothelial cells	Investigation of senescence and the relation between *FXN* expression and pulmonary hypertension	Culley et al. (2021)
FRDA iPSC-derived beta cells	Low *FXN* levels in FRDA iPSC-derived beta cells, upregulation of it *via* glucagon-1-peptide treatment	Igoillo-Esteve et al. (2015), Igoillo-Esteve et al. (2020)

cerebellum and brainstem are observed (Apolloni et al., 2022; Khan et al., 2022). Non-neurological symptoms include hypertrophic cardiomyopathy, glucose intolerance, and diabetes mellitus (Campuzano et al., 1996; Gottesfeld, 2019). Foot deformity and scoliosis are the early signs of this disease in some cases. In others, cardiomyopathy is the first clinical symptom (Pandolfo, 2009). Diabetes mellitus usually develops in the later stage (De Michele et al., 1996).

GAA repeat expansions lead to a reduction in frataxin protein levels to 5–35% (Gellera et al., 2007; Abruzzo et al., 2013; Bürk, 2017; Vannocci et al., 2018). Why GAA repeat expansion leads to a reduction in frataxin protein levels and the role of frataxin in FRDA pathologies remain unclear. Likewise, the molecular pathology of cardiomyopathy in FRDA is not entirely elucidated, even though the most common cause of death is cardiomyopathy (Crombie et al., 2017). There are neither effective therapeutics for this disease nor any drugs that can slow its progression (Strawser et al., 2014). Therefore, modeling approaches are crucial. However, the selection of suitable models is an important step. The selected model should appropriately reflect FRDA pathophysiology.

Animal models have been nicely covered (Perdomini et al., 2013), whereas recent reviews about the molecular pathways involved in FRDA progression have been discussed in detail (Gottesfeld, 2019). In this perspective article, we focused on the challenges of FRDA *in vivo* (both non-complex and complex organisms) and patient-derived models and discussed iPSC-based models more comprehensively.

In vivo models of FRDA include yeast, nematode worm, fruit fly, and mice (Babcock et al., 1997; Radisky et al., 1999; Puccio et al., 2001; Al-Mahdawi et al., 2004; Vázquez-Manrique et al., 2006; Virmouni et al., 2014; Monnier et al., 2018), whereas FRDA *in vitro* models include patient-derived cells such as immortalized lymphoblastoid cells, primary fibroblasts (Li et al., 2016; Agro and Diaz-Nido, 2020; Misiorek et al., 2020; Johnson et al., 2021), FRDA-derived iPSCs (Angulo et al., 2021; Kelekci et al., 2021), and iPSC-based models such as neurons, cardiomyocytes, and beta cells (Crombie et al., 2016; Schreiber et al., 2019) (Figure 1). All these FRDA models need to imitate the symptoms of FRDA patients. For instance, they should be exhibiting a progression of sensory ataxia and/or cardiomyopathy due to reduced frataxin protein level, ideally as a result of GAA expansions in the first intron of the *FXN* gene (Perdomini et al., 2013).

Challenges of Friedreich's ataxia *in vivo*, and patient-derived models

The genetic basis of FRDA makes it challenging to study *in vivo*. In mice, knockout of the *FXN* gene is embryonically lethal (at E 6.5) (Cossee, 2000). Therefore, conditional knockout FRDA

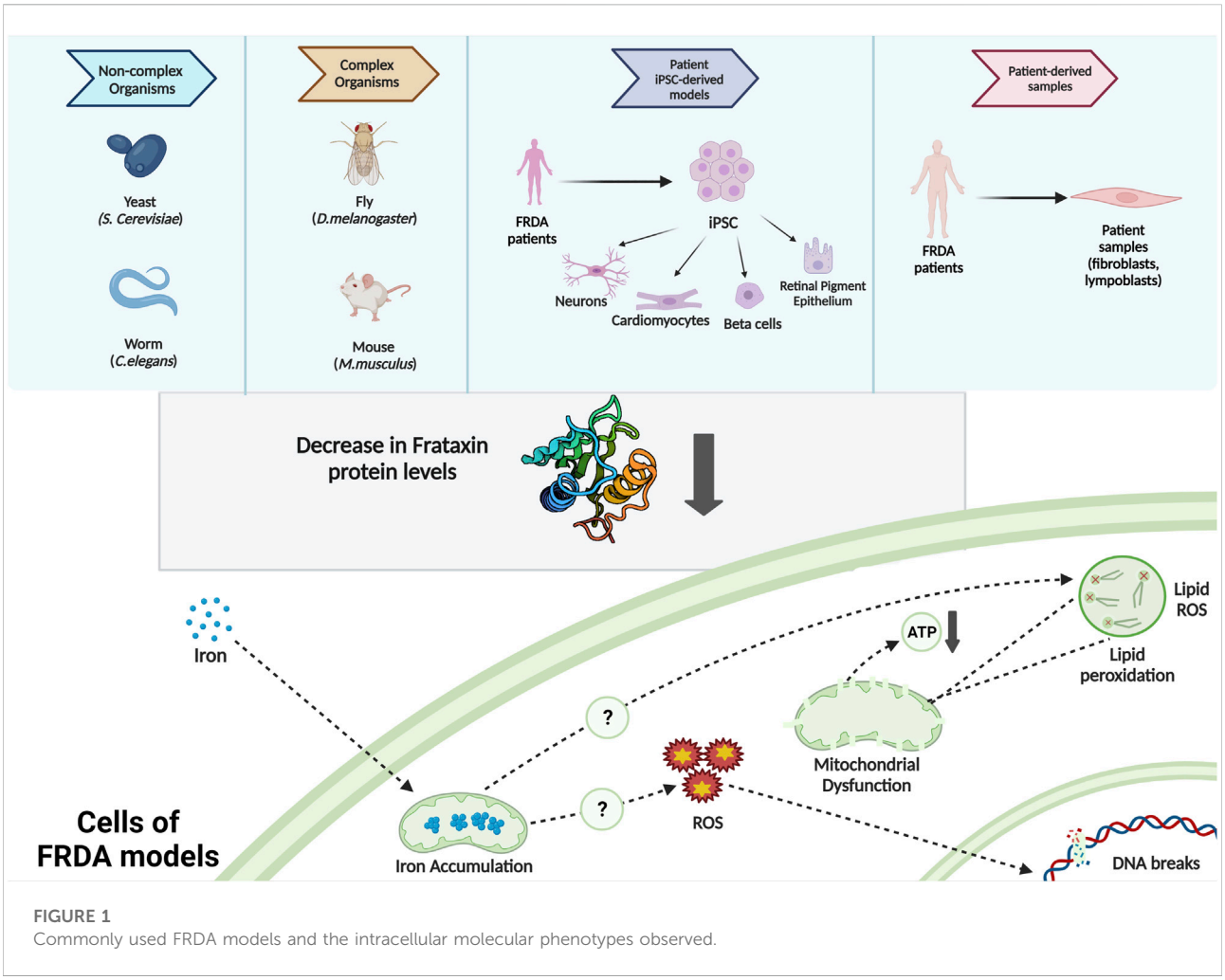

FIGURE 1
Commonly used FRDA models and the intracellular molecular phenotypes observed.

mouse models were generated. Expression of Cre recombinase was induced under *MCK* (muscle creatine kinase, a gene expressed in the heart cells) and *NSE* (neuron-specific enolase, a gene expressed in the neurons) promoters (Puccio et al., 2001; Puccio, 2009). Along with developing cardiomyopathy, MCK mice exhibited ISC enzyme deficiencies and iron accumulation at the early stages (Puccio, 2009; Simon et al., 2004). NSE mice developed progressive ataxia with a loss of proprioception (Simon et al., 2004; Perdomini et al., 2013). Additionally, a reversible frataxin knockdown mouse model was developed, and it had cardiac conduction defects, degeneration of dorsal root ganglia, and early mortality (Chandran et al., 2017). Although conditional models reproduce most of the characteristic features of FRDA, they cannot accurately model the effects of genetic background. Moreover, conditional models lead to a complete loss of frataxin, but in FRDA patients, partial frataxin deficiency is observed (Puccio, 2009; Perdomini et al., 2013).

GAA insertion models were also developed. Y4R and YG8R were generated by inserting expanded $(GAA)_{90}$ and $(GAA)_{190}$ alleles, respectively. Both express only human frataxin (Al-Mahdawi et al., 2004; Al-Mahdawi et al., 2006; Perdomini et al., 2013). The frataxin protein level was 57% in YG8R, which exhibited mild progressive motor coordination deficits (Al-Mahdawi et al., 2006; Clark et al., 2007; Martelli et al., 2012). Later, YG8sR mice were generated from YG8R. YG8sR mice have a single copy of the *FXN* transgene and a single $(GAA)_{120}$ repeat expansion mutation. They exhibited behavioral deficits along with decreased expression of *FXN*, and reduced aconitase activity in brain regions (Anjomani Virmouni et al., 2015).

However, the short life span of *in vivo* models leads to incomplete development of pathological hallmarks. Also, although there is physiological accordance between humans and rodents, there are genomic differences that result in profound implications in disease modeling (Dawson et al., 2018). Therefore, further studies on FRDA animal models to overcome these challenges and thereby represent the disease phenotype better and faster are needed.

In 1999, human FRDA primary fibroblasts were used to understand whether this cell type is a reasonable model to study

GAA expansions and to test potential therapeutic drugs. The fibroblasts had reduced levels of frataxin mRNA and were more sensitive to ROS-inducers (A. Wong, 1999). This study led FRDA fibroblasts and lymphoblastoid cells to be used in understanding FRDA phenotypes and investigating the effect of potential therapeutic agents. Although primary fibroblasts and lymphoblastoid cells are easily accessible, they are not the main cell types affected in the course of FRDA and they may not represent the phenotypes of FRDA adequately (Perdomini et al., 2013). Georges et al. (2019) showed that resveratrol, an antioxidant drug, and nicotinamide, vitamin B3, did not induce a significant increase in frataxin protein levels in FRDA iPSC-based neurons, although both drugs were shown to increase frataxin mRNA levels in fibroblasts and lymphoblastoid cells of FRDA patients. Additionally, one has to keep in mind that there are limited sources to work with fibroblasts because they do not grow indefinitely. Therefore, in this perspective article, we did not focus on studies where these patient-derived cells were used.

To summarize, model organisms and patient-derived cells can be used to model FRDA, but due to the technical and biological limitations, there is a need for more human FRDA-like models such as FRDA iPSC-based cells or organoids.

Generation of patient-specific induced pluripotent stem cells

The discovery that exogenous expression of *OCT4, SOX2, KLF4,* and *c-MYC* can reprogram mammalian somatic cells back to an embryonic-like state (Takahashi and Yamanaka, 2006) enabled scientists to generate disease-specific pluripotent stem cell lines (Soldner and Jaenisch, 2018). As iPSCs can be autologous, they can replace embryonic stem cells in the field of clinical applications of cellular replacement therapies and screening for potential pharmaceuticals (Onder and Daley, 2012). The first iPSC-based disease model was familial amyotrophic lateral sclerosis (ALS) (Dimos et al., 2008). Since then, iPSC-based disease models have been developed to study a diverse set of neurological diseases, such as spinal muscular atrophy (SMA) (Ebert et al., 2009), Rett syndrome (Marchetto et al., 2010), and Friedreich's ataxia (Ku et al., 2010).

Impact of Friedreich's ataxia-derived induced pluripotent stem cells and induced pluripotent stem cell-based models on Friedreich's ataxia research

In 2010, iPSCs were generated from fibroblasts of FRDA patients for the first time. *FXN* downregulation observed in fibroblasts was found to be retained in the iPSCs (Ku et al., 2010). Since then, several additional FRDA patient-derived iPSCs were generated to study the pathophysiology of this disease (Liu et al., 2011; Bolotta et al., 2019; Schreiber et al., 2019; Dionisi et al., 2020; Mazzara et al., 2020; Angulo et al., 2021; Kelekci et al., 2021).

Modeling GAA repeat instability with induced pluripotent stem cells

When the first FRDA-derived iPSCs were generated, genomic instability during reprogramming and culturing of iPSCs was observed (Ku et al., 2010; Sharma, 2002). The reason for GAA repeat instability in iPSCs was due to elevated expression levels of mismatch repair enzymes (MSH2, MSH3, and MSH6) (Jintang Du et al., 2012). Defects in replication fork progression and stalling in the 3′–5′ direction were also observed during the replication of *FXN* (Gerhardt et al., 2016). Interestingly, treatment of FRDA fibroblasts with certain epigenetic drugs such as sodium butyrate (NaB), an HDAC class I inhibitor, and Parnate, a LSD1 inhibitor, led to decreased repeat instability during reprogramming. These compounds increased *FXN* gene expressions (Polak et al., 2016).

Recently, DNA methylation patterns on GAA repeats were studied. FRDA-specific differentially methylated regions (DMRs) were found to be closer to GAA repeats in FRDA iPSC-based models. Interestingly, the prevalence of *FXN* genes that lack FRDA-specific hypomethylation (unmethylated epialleles) was found to be a predictor of *FXN* expression and age of onset of FRDA (Rodden et al., 2021). However, the reason for the absence of unmethylated epialleles in GAA repeats near the *FXN* gene and the effect of methylation on GAA expansion remains to be elucidated.

Considering all these, further studies are necessary to understand the mechanisms behind the repeat expansions and repeat instability observed in FRDA iPSCs. Specifically, the effect of mismatch repair enzymes, the role of methylation in the repeats, and the reason for replication fork stalling should be further investigated in the future.

Modeling of Friedreich's ataxia phenotypes using induced pluripotent stem cell-based models

Decrease in frataxin expression causes iron accumulation, impaired iron–sulfur cluster biogenesis, increased oxidative stress, mitochondrial dysfunctioning (Calap-Quintana et al., 2018; Gonzalez-Cabo & Palau, 2013; Santos et al., 2010), and ferroptosis (Cotticelli et al., 2019; La Rosa et al., 2020; Turchi et al., 2020; Terzi et al., 2021). These phenotypes were also recapitulated in iPSC-based *in vitro* models of FRDA (Schreiber et al., 2019). Here, we highlight recent studies utilizing FRDA iPSC-based models (Table 1).

FRDA iPSC-based neurons exhibited reduced mitochondrial transcripts and altered expression levels in transcripts involved in

ECM organization and focal adhesion (Lai et al., 2019). Primary proprioceptive neurons differentiated from FRDA iPSCs had reduced expression of proprioceptor-specific markers and exhibited shorter survival *in vitro* (Dionisi et al., 2020).

FRDA iPSC-derived cardiomyocytes (FRDA iPSC-Cms) showed decreased levels of frataxin and mitochondrial potential and impaired functioning of mitochondria (Hick et al., 2013). Lee et al. (2014) exposed FRDA iPSC-Cms to iron-overloading conditions, and this resulted in hypertrophic cardiac stress responses, iron accumulation, and an increase in ROS formation. FRDA iPSC-Cms had calcium handling deficiencies (Crombie et al., 2017). They also exhibited lipid droplet accumulation (J. Li et al., 2019).

FRDA iPSCs were differentiated into endothelial cells, as well. FRDA iPSC-based endothelial cells (iPSC-ECs) exhibited decreased proliferative activity along with an increase in the expression of cellular senescence markers. Forced *FXN* expression in FRDA iPSC-ECs did not rescue this phenotype, showing that this senescence phenotype is irreversible (Culley et al., 2021).

FRDA iPSC-based β cells were generated in 2019, and those cells had lower *FXN* gene expression. However, FRDA iPSC-based β cells had functional mitochondria and functional secretion of glucose-induced insulin (Igoillo-Esteve et al., 2020).

Therapeutic solutions for Friedreich's ataxia with the help of induced pluripotent stem cell-based technologies

Heterochromatin formation around the *FXN* gene is the major reason for the downregulation of the *FXN* gene in FRDA (Chutake et al., 2014; Kumari et al., 2011). Histone deacetylation, DNA methylation, and heterochromatin mark (H3K9me3 and H3K27me3) were detected around the *FXN* gene (Al-Mahdawi et al., 2008). Therefore, epigenetic regulators such as HDAC inhibitors have been studied using FRDA iPSC-based *in vitro* models (Zhang et al., 2019). HDAC inhibitor treatment of FRDA iPSC-based neurons resulted in a significant increase in *FXN* levels along with a decrease in oxidative stress response (Codazzi et al., 2016). More recently, large-scale chemical screens on FRDA iPSC-based neuronal progenitor cells containing a *FXN* reporter system revealed HDAC inhibitors as the only compounds that could upregulate *FXN* levels (Schreiber et al., 2022).

Recent advances in genome editing enabled the correction of expanded alleles in FRDA. Three-fold higher expression of frataxin in both mRNA and protein levels was observed in FRDA iPSC-based neurons after zinc finger nuclease (ZFN)-mediated excision of expanded GAA repeat regions (Li et al., 2015). In addition, an increase in aconitase activity and ATP levels was observed (Li et al., 2015). Similarly, GAA expanded repeats were excised using ZFNs in FRDA iPSC-based cardiomyocytes, which resulted in the upregulation of frataxin expression, a decrease in lipid droplet accumulation, and a decrease in the expression of cardiac hypertrophy-related genes (J. Li et al., 2019). Recently, dorsal root ganglia organoid-derived sensory neurons were generated from FRDA iPSCs. When the entire *FXN* intron 1 was excised using CRISPR-Cas9, cellular and molecular deficits observed in these organoids were rescued. This effect was not observed when only the expanded regions were removed in those organoids (Mazzara et al., 2020). All of these studies show that nuclease-mediated removal systems can be used to rescue FRDA phenotypes in the future.

Recently, repeat-targeted nucleic acids (L. Li et al., 2016; Shen et al., 2019; Shen et al., 2020) and synthetic transcription elongation factors (Syn-TEFs) (Erwin et al., 2017) were used to elevate *FXN* expression in FRDA iPSC-based models. In addition, particle-mediated delivery of frataxin-encoding plasmid DNA has been used to increase *FXN* levels in FRDA iPSC-based sensory neurons (Czuba-Wojnilowicz et al., 2020). Oligonucleotides targeting 5′ and/or 3' untranslated regions of the *FXN* transcript increased *FXN* mRNA and protein levels in FRDA iPSC-based neuronal progenitor cells (Belbellaa et al., 2020). Taken together, these studies show that overexpression of *FXN* can have therapeutic potential, but further optimization is required.

Discussion and future perspectives on Friedreich's ataxia models

FRDA is a rare neurodegenerative disorder, mediated by triplet repeat expansion which results in the downregulation of frataxin. In the recent years, there have been considerable efforts to find a promising drug for FRDA. Therapeutic approaches to augment frataxin production or modulate mitochondrial malfunctioning, increase ROS production, and Nrf2 activation have been used in phase II clinical trials (Rodden & Lynch, 2021). Additionally, there are many studies addressing potentially promising therapeutic approaches for FRDA pathophysiology. For instance, smoothened agonist (SAG) treatment in *FXN* knockdown human astrocytes resulted in increased neuron viability, neurite length, and synapse formation when these cells were injected into the mice brain (Vicente-Acosta et al., 2022). Additionally, Cur@SF, which are nanospheres containing curcumin in silk fibroins, reduced the levels of ROS in FRDA patient-derived fibroblasts and reduced FRDA phenotypes in YG8R mice models (Xu et al., 2022). Lastly, after eight single FDA-approved drugs were tested on FRDA fibroblasts, dimethyl fumarate and resveratrol treatments were shown to increase *FXN* mRNA levels. The combination of these two drugs also increased rotarod performance in FRDA mice models (Abeti et al., 2022). However, all these promising drugs should be further tested in FRDA iPSC-derived neurons and cardiomyocytes as these cells are the main cell types affected in FRDA.

In this perspective article, we have discussed recent models of FRDA and their contributions to identify molecular mechanisms in FRDA development and develop potential therapeutics through drug screening and gene therapy studies. Animal models are composed of nematode worms, fruit flies, and mice. Many of these models were successful in recapitulating the FRDA phenotypes *in vivo*. However, the general concern about the animal models of FRDA is the difficulty in creating such models that are able to exhibit all FRDA-related symptoms and the cellular phenotypes due to reduced *FXN* levels resulting from GAA repeat expansion. *In vitro* models include primary cells, genetically modified cell lines (Perdomini et al., 2013), iPSC-based cells (Schreiber et al., 2019), and, recently, organoids (Mazzara et al., 2020). Consideration of models using primary patient-derived fibroblasts and lymphoblastoid cells remains to be controversial because these cells are disease-irrelevant. Differentiated FRDA-derived iPSC-based models exhibit gene expression profiles that are significantly different from the isogenic iPSC-based models created and show similar phenotypes observed in patients' cells (Lai et al., 2019). Therefore, FRDA iPSC-based models can be considered promising models for future FRDA studies. However, FRDA-derived iPSC *in vitro* models have certain limitations as well. First is the repeat instability observed during the reprogramming and culturing duration of FRDA-derived iPSCs. This limitation may potentially be overcome by using therapeutic agents that may prevent this instability. Another challenge is the lack of paired isogenic lines. In the case of FRDA-derived iPSCs, isogenic derivatives can be created simply *via* the excision of repeats. Lastly, it may not be possible to study tissue and organ level phenotypes observed in FRDA patients *via* 2D differentiated cells. iPSC-based organoids provide an alternative in this regard. Nevertheless, thanks to FRDA iPSC-based models, the reasons behind GAA repeat expansion and mechanisms of disease-relevant phenotypes were studied thoroughly and efficient therapies using CRISPR/Cas9 to increase *FXN* expression were investigated over the past decades. However, there are still many open questions that need to be addressed and challenges to overcome.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding authors.

Author contributions

Contributed substantially to the conception or design of the work: SK and AY. Drafted the manuscript: SK, AY, and KS. Revision of the manuscript for important intellectual content: SK, AY, KS, DÇ, and TÖ. All authors approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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