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Review

Fibroblast growth factor 21 and autophagy: A complex interplay in Parkinson disease

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ABSTRACT

Parkinson disease (PD) is the second common neurodegenerative disorder after Alzheimer's disease (AD). The predominant pathological hallmark is progressive loss of dopaminergic (DA) neurones in the substantia nigra (SN) complicated by aggregation of misfolded forms of alpha-synuclein (α-syn). α-syn is a cytosolic synaptic protein localized in the presynaptic neuron under normal circumstances. What drives misfolding of this protein is largely unknown. However, recent studies suggest that autophagy might be an important risk factor for contributing towards PD. Autophagy is an evolutionarily conserved mechanism that causes the clearance or degradation of misfolded, mutated and damaged proteins, organelles etc. However, in an aging individual this process might deteriorate which could possibly lead to the accumulation of damaged proteins. Hence, autophagy modulation might provide some interesting cues for the treatment of PD. Additionally, Fibroblast growth factor 21 (FGF21) which is known for its role as a potent regulator of glucose and energy metabolism has also proved to be neuroprotective in various neurodegenerative conditions possibly via mediation of autophagy.

1. Introduction

Parkinson disease (PD) is a progressive and an age-dependent neurodegenerative disorder that predominantly affects the dopaminergic (DA) neuronal system in the substantia nigra (SN) region of the brain causing its deterioration over time. This deterioration gives rise to motor abnormalities in a PD affected patient causing tremor, bradykinesia, akinesia, postural instability, slurred speech etc. Recent research also enlightened that occurrence of non-motor dysfunctions in an individual initiate in the advanced stage of PD. It comprises mainly of cognitive dysfunction, constipation, sleep disorder, depression, anxiety etc. PD is known to affect at least 0.3% of the worldwide population and over 3% of those over 80 years of age. The predominant pathological hallmark of PD is aggregation of misfolded forms of alpha-synuclein (α-syn) in intraneuronal inclusions known as lewy bodies (LBs) in cell soma and in lewy neurites (LNs) in neuronal processes. α-syn is a presynaptic protein involved in neurotransmission. It is normally degraded by ubiquitin-proteasome system (UPS) and autophagy-lysosome

Abbreviations: AD, Alzheimer's Disease; AKT, Protein kinase B; ALS, Autophagy-lysosome system; ATF, Activating transcription factor; ATG, Autophagy related gene; ATP, Adenosine triphosphate; BAT, Brown adipose tissue; BBB, Blood brain barrier; CHOP, C/EBP homologous protein; ChREBP, Carbohydrate response element-binding protein; CMA, Chaperone mediated autophagy; CNS, Central nervous system; CREBH, cAMP-responsive element-binding protein H; CSF, Cerebrospinal fluid; DA, Dopaminergic; DJ-1, Protein deglycase-1; ELF2-α, E74 Like ETS Transcription Factor 2-α; ER, Endoplasmic reticulum; FGF21, Fibroblast growth factor 21; FGFR1, FGF receptor 1; FRS2α, FGFR substrate 2 alpha; FXR, Farnesoid X receptor; GR, Glucocorticoid receptor; HIF-1, Hypoxia Inducible Factor-1; ICV, Intracerebroventricular; iPSC, Induced pluripotent stem cell; IRE, Inositol-requiring enzyme; ISR, Integrated stress response; LAMP-2A, Lysosome-associated membrane glycoproteins 2a; LB, Lewy bodies; LC3, Light Chain 3; LN, Lewy neurites; LRRK2, Leucine rich repeat kinase 2; LXR, Liver X receptor; MAPK, Mitogen-activated protein kinases; MPP+, 1-methyl-4-phenylpyridinium; mRNA, Messenger ribonucleic acid; mtDNA, Mitochondrial deoxyribonucleic acid; mTORC1, Mechanistic target of rapamycin complex 1; NAFLD, Non-alcoholic fatty liver disease; ORF, Open Reading Frame; PD, Parkinson Disease; PDD, Parkinson disease dementia; PERK, PKR-like ER kinase; PINK-1, PTEN induced kinase-1; PPARγ, Peroxisome Proliferator activated Receptor γ; Rab, Ras-Related Protein; RARβ, Retinoic acid receptor beta; REM, Rapid eye movement; ROR, Retinoic acid receptor-related orphan receptor; siRNA, Small interfering ribonucleic acid; SN, Substantia Nigra; SNCA, Synuclein alpha; UPR, Unfolding Protein Response; UPR^{mt}, Mitochondrial UPR; UPS, Ubiquitin-proteasome system; UTR, Untranslated region; Vps35, Vacuolar protein sorting 35; WAT, White adipose tissue; α-syn, Alpha-synuclein; β-Klotho, Beta-klotho

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system (ALS) [1]. UPS is responsible for the selective degradation of short-lived proteins and its dysfunction leads to the activation of ALS [2]. Exceptionally high affinities of the mutant forms of α-syn blocks the lysosomal uptake and inhibits its degradation via ALS [1]. This very well explains that ALS dysfunction is an important mechanism in neurodegeneration especially PD. Subsequently, blockage of ALS can aggravate various factors that can further complicate PD, the most important being endoplasmic reticulum (ER) stress [3]. ER stress is mainly a compensatory mechanism that is intended to preserve cellular function and neuronal survival [4] by activating PKR-like ER kinase (PERK), activating transcription factor(ATF)-6, inositol-requiring enzyme(IRE)-1 [5]. Phosphorylation of eukaryotic initiation factor 2-α (eIF2α), via activation by PERK, leads to translational induction of ATF4. Several studies have proved that stressors like starvation, autophagy dysfunction activates ATF4 which is also known to upregulate Fibroblast growth factor 21 (FGF21) [6].

2. Fibroblast growth factor 21

FGF21 belongs to the FGF superfamily consisting of 23 members till date that is solely involved in performing functions like cell growth, differentiation, wound healing, neuronal development, and angiogenesis [7]. FGF21 is a secreted protein comprised of 210 amino acid and a hydrophobic amino terminus. FGF21 mainly acts through its classical co-receptor beta-klotho (β-Klotho) and FGF21 receptor 1 (FGFR1). FGF21 is highly expressed in the liver [8], pancreas, adipose tissue etc. In the brain, FGF21 can cross the blood brain barrier (BBB) and portrays a high penetration capacity as its co-receptor β-Klotho lacks the classical heparin binding domain [9]. FGF21 has long been known for its action as a potent anti-diabetic hormone facilitating improved glucose and triglyceride levels in obese mice [10], augmented ketone body formation and fatty acid oxidation [11] etc. FGFRs are expressed in low levels in various regions of the brain and in the liver. FGF21 actions are mainly mediated through brain especially during gluconeogenesis. FGF21 expressions in the cerebrospinal fluid (CSF) are linear with the serum level of FGF21. The central actions of FGF21 are mainly an increased sympathetic activity that accounts for increased energy expenditure. In a study, the FGF21 transgenic (β-Klotho floxed/ Camk2a-Cre) mouse model showed a decreased energy expenditure and increased weight gain even on standard chow diet. Moreover, the mice that lack brain β-Klotho reported reduced sympathetic nerve activity in brown adipose tissue (BAT), which was reversed on intracerebroventricular (ICV) injection of FGF21 [12]. In another study the central administration of a low dose of FGF21 found BAT activation and browning of inguinal fat through sympathetic activation which was measured by the norepinephrine turnover [13]. These evidences suggest that the presence of FGF21 receptor in the brain accounts in all the central metabolic actions of FGF21. The fact that FGF21 can foster miracles in ablating PD pathology by an appropriate manipulation of autophagy can be an attractive area of research in the future. Apart from FGF21, two other members that have recently shown relevance in PD pathology are FGF2 and FGF20. FGF20 is a neurotrophic factor for rat midbrain DA neurons [14]. Symptom alleviation related to PD was observed when neurons were treated with exogenous FGF20 and FGF2 after monkey stem cells differentiated in vitro into DA and transplanted into a primate PD model [15]. FGF20 has shown promising answers in stem cell biology in vitro although it shows some negative result for PD aetiology in vivo. Although in the classical FGF signalling axis, the FGFR stimulates the FGFR tyrosine kinase in turn activating Protein kinase B (AKT) and Mitogen-activated protein kinases (MAPK) pathways in a FGFR Substrate 2 alpha (FRS2α) dependent manner which is known to suppress autophagy leading to inhibition of cardiac progenitor cell differentiation. But involvement of all the other members of the FGF superfamily in autophagy modulation in PD pathology is not yet established.

3. PD pathology

PD is the second most common neurodegenerative disease, affecting at least 0.3 % of the worldwide population and over 3% of those over 80 years old [16]. Much has been discovered about the underlying etiology of PD, since James Parkinson's essay on the Shaking Palsy over 200 years ago [17]. The cardinal features of PD primarily characterized as a range of slowness of movement, rigidity, postural instability and tremor in addition to non-motor symptoms including cognitive anomaly, rapid eye movement (REM) sleep disorder, constipation and hyposmia. Loss of DA neurons in the SN and its downstream dysregulation of basal ganglia activity contribute to the appearance of motor symptoms [18]. Besides, during the disease progression, up to 80 % of PD patients will also experience a form of dementia known as Parkinson disease dementia (PDD) [19] And it is believed that non motor symptoms particularly cognitive abnormality may either precede way before the onset of motor symptoms or can develop as the disease progresses [20]. In addition to this, it should also be highlighted that PD is comprised of two forms familial and sporadic. Friedrich Lewy in 1912 described that PD and PDD are neuropathologically characterized by the presence of proteinaceous inclusions termed LBs. Continued research led to the identification of a synaptic protein, α-syn as the primary component of LBs. The discovery that mutations in synuclein alpha (SNCA) gene cause familial forms of PD put forth the hypothesis that α-syn plays a direct role in disease pathogenesis. Mutations in specific proteins/genes encoding α-syn like PTEN induced kinase-1 (PINK-1), protein deglycase-1 (DJ-1) and Leucine rich repeat kinase 2 (LRRK2) etc also contribute towards PD pathogenesis. While the etiology for the sporadic form encompasses genetic and environmental factors but still in many cases it remains largely unknown. In addition to this, the Braak's hypothesis states that an unknown pathogen such as a virus or bacterium is known to enter the gut via the nasal cavity initiating lewy pathology in the gut [21]. This could be a likely mechanism for the initiation of sporadic PD. Here, the olfactory tract and the vagal nerve represents an important link in the spreading of PD pathology. PD is classified as α-synucleinopathy based on the pathological and genetic data implicating α-syn in these diseases. Understanding how α-syn aggregates and leads to neuronal dysfunction and death in vulnerable neurons have always been the major area of focus in the field of PD. Growing evidence pinpoints that stochastic formation of LBs in individual neurons is not sufficient to explain the pathology and symptomatic progression observed in PD. Rather, prion like spread and cell-to-cell transmission of misfolded α-syn represents a more broader picture. Pathologically, these misfolded form of α-syn is released by one neuron and taken up by another and can also act as a template in the recipient neuron. However, the pathological mechanisms about the aggregation, propagation, clearance or prevention of the degeneration of infected neuronal cells is still under investigation.

α-syn is a cytosolic protein and under normal circumstances it can be found in the presynaptic terminal. Pathological conditions aggravate α-syn to form LBs in the soma of affected neuron [18]. PD is an age-related disease and the observations that LB can affect only a subset of neurons suggest that α-syn inclusions may form over long periods and thereby lead to the death of the infected neurons [22]. However, recent data from humans and model system indicates that α-syn can also affect neuron in a manner corresponding cell-to-cell transmission where the inclusions might be taken up by synaptically-connected neurons, leading to a pathological spread through the brain that correlates with disease progression. The various contributing factors and signalling pathways that account for the DA neuronal degeneration in PD is schematically represented in Fig. 1.

In addition to misfolding, aggregation and mutations in the proteins that cause PD, many studies have also found that deterioration of a self-conserved mechanism, autophagy, with age may also lead to accumulation of these mutated or misfolded proteins resulting in neuronal death. Autophagy is by far regarded as one of the major contributing

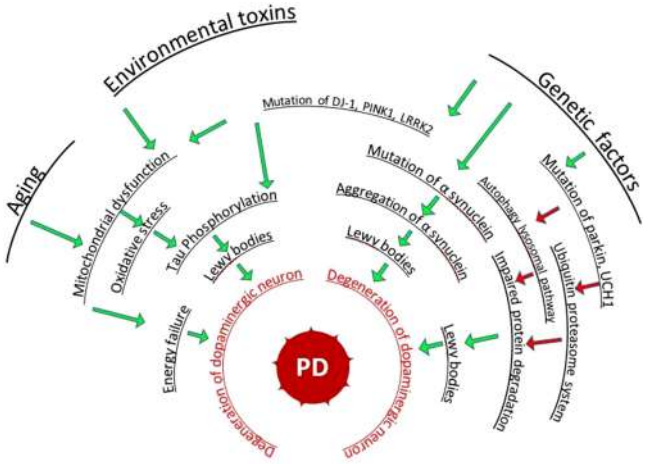

Fig. 1. Schematic diagram representing various factors and pathways involved for the degeneration of DA neurons.

factor in diseases like neurodegeneration, cancer, metabolic disorders etc.

3.1. Interplay between autophagy and PD

A major factor that can prove to be an important risk factor in neurodegenerative conditions is dysfunctional autophagy. Autophagy is primarily meant to clear damaged, unwanted and misfolded proteins and once it fails to do so, it results in a build-up of the damaged proteins causing a toxic insult to the neurones. Studies have very well proved that apart from neurodegeneration, autophagy dysfunction is very crucial for the occurrence of several other diseases like cancer, metabolic disorders etc. Autophagy related gene (Atg)-7 is a very important regulator of autophagosome formation and its conditional deletion in midbrain DA neuronal model, led to motor abnormalities [23]. As, α-syn is also degraded by chaperone mediated autophagy (CMA) in vitro [1], it is possible that PD linked- Vacuolar protein sorting 35 (Vps35) can lead to α-syn accumulation via lysosome-associated membrane glycoproteins 2a (LAMP-2A) deficiency as evidenced by a deleted VPS35 mice model [24]. In an idiopathic PD brain, levels of CMA markers down regulated that correlates with α-syn accumulation suggesting that ALS plays a critical role in PD [25,26]. Although mutant forms of α-syn mainly A30 P and A53 T binds with high affinity to LAMP-2A but fails to translocate resulting in discrepancy in a part of CMA machinery [1]. Also, the degradation rate for the mutated proteins are quite slow as compared to the wild type proteins [27]. Some of the other evidences that link autophagy dysfunction with PD is that α-syn decreases autophagosome formation by impeding the function of Ras-related protein-1a (Rab-1a) and Atg 9 [28]. One of the most common LRRK2 mutation G2019S (LRRK2G2019S) in PD blocks CMA in an exact similar manner like α-syn i.e. via LAMP-2A blockade [29]. LRRK2 mediated vesicular trafficking and autophagic flux [30] can be explained by the fact that it has recently been linked to the phosphorylation of the trafficking mediator rab10 [31]. Rab 10 is involved in autophagic degradation of lipids in addition to its role in trafficking between the trans-golgi network and the plasma membrane [32]. Immunofluorescence studies using induced pluripotent stem cell (iPSC) derived neurons of patients and LRRK2-PD (LRRK2G2019S) depicted an upregulation of Light Chain 3 (LC3) positive puncta and p62 compared to controls. Further, electron microscopy was performed in the same study that showed an increase in autophagic vacuoles, lipid accumulation, and dilated ER in PD-derived neurons [33]. Hence, majority of the studies point towards the deleterious effect that is brought upon by disrupted autophagy machinery, however, it should be noted that autophagy failure causes ER stress that ultimately activates a transcription factor known as ATF4 that serves the purpose of preserving neuronal survival and health during stress. ATF4 is also known to activate FGF21 that possess remarkable neuroprotective effect as is claimed by various animal studies. Although the notion that FGF21 elicits neuroprotective effect by regulating autophagy is still in its infancy but the direct signalling mechanism between FGF21 and ATF4 gives hope for future clinical trials.

4. FGF21 regulation by transcription factors involved in autophagy

FGF21 is an endocrine hormone which is widely known for its role to regulate glucose and energy metabolism in the body. It acts in conjunction with its co-receptor β-Klotho and FGFR1. This hormone was unknown until 2005 when it was demonstrated that FGF21 administration reduced plasma glucose and triglycerides to an almost normal level in both ob/ob and db/db mice [34]. In our previous review, a detailed overview of FGF21 and its basic mechanism of metabolic regulations, beneficial effect on neurodegenerative conditions associated with metabolic stress are well described [35]. In hepatocytes, FGF21 is regulated by the Unfolding Protein Response (UPR) [36,37]. This was confirmed when it was observed that FGF21 increased in the liver of patients suffering from steatosis, and mouse models of obesity or non-alcoholic fatty liver disease (NAFLD) where at the same time ER stress was triggered. This led to the confirmation that FGF21 expression was dependent on PERK– (E74 like ETS transcription factor 2- α) eIF2α – ATF4 pathways both, in vitro and in vivo [37]. Moreover, ER stress markers was induced in genes in FGF21-null mice with rapid lipid accumulation in the liver after treatment with an inhibitor of glycoprotein biosynthesis, tunicamycin that promotes ER stress [37]. Several studies have suggested that hepatic FGF21 expression is also under the regulation of other transcription factors.

The thyroid hormone receptor β, which mediates the action of triiodothyronine in the liver induces FGF21 activating lipolysis, and hepatic fatty acid oxidation [38]. Moreover, retinoic acid receptor beta (RARβ) also regulates FGF21 expression [39–42]. A recent in vitro study in C2C12 [43] showed that the metabolic effect of the RARb ligand, retinoic acid are similar to FGF21, but is yet to be confirmed in vivo.

Retinoic acid receptor-related orphan receptor (ROR)-α has been implicated in various physiological functions, including the immune system, inflammation, and circadian rhythms. In C2C12 myotubes, the synthetic RORα/γ agonist SR1078 stimulated the production and gene expression of FGF21. RORα-silenced cells showed weaker expression of messenger ribonucleic acid (mRNA) and secretion of FGF21 as compared to cells transfected with non-targeting control small interfering ribonucleic acid (siRNA). In C2C12 myotubes, SR1078 significantly upregulated a potent marker of ER stress, C/EBP homologous protein (CHOP), in a dose-dependent manner, while C2C12 cells silenced with RORα, reduced CHOP expression suggesting that RORα is involved in the regulation of FGF21 expression and stimulates ER stress in C2C12 myotubes. Other reports have shown that glucocorticoid receptor (GR) [44], cAMP-responsive element-binding protein H (CREBH) [45], carbohydrate response element-binding protein (ChREBP) [46], Peroxisome Proliferator activated Receptor γ (PPARγ) [47,48], farnesoid X receptor (FXR) [49], and liver X receptor (LXR) [50,51] regulates the hepatic FGF21 expression either positively or negatively. FGF21 regulation in extrahepatic tissues like skeletal muscle, white adipose tissue (WAT) and BAT is accomplished via different transcription factors. In WAT, PPARγ activation increases FGF21 production where it acts as an autocrine or endocrine factor to improve insulin action [52]. FGF21 is regulated by ATF2 in BAT [53] while in skeletal muscle ATF4 [54] and the PI3K–AKT signaling pathway controls FGF21 expression [55].

Recent studies in C. elegans and mammals implied that mitokines are required for intercellular communication from neurons with dysfunctional mitochondria. Activation of the mitochondrial UPR (UPR^{mt})

on peripheral cells, such as the intestinal cells, are facilitated by mitokine(s) [54,56–58]. For example, a interneuron secreted neuropeptide, FLP-2, activates the UPR^{mt}, by signalling in intestinal cells upon neuronal induction of mitochondrial stress [58]. Similarly, in mammalian systems, integrated stress response (ISR) regulator ATF4 induces FGF21 in multiple mammalian tissues, during mitochondrial stress caused by autophagy deficiency [54,59]. Additionally, dysfunctional mitochondria are manifested in several incurable diseases [60]. For e.g., mitochondrial deoxyribonucleic acid (mtDNA) mutations causes mitochondrial myopathy, a progressive disease associated with defective respiratory chain function and muscular abnormalities [61]. A recent study showed the link between mechanistic target of rapamycin complex 1 (mTORC1) and UPR^{mt} regulation. The kinase, mTORC1 with S6 as its downstream effector controls nutrient availability, adenosine triphosphate (ATP) production, and regulates protein synthesis [62]. Mitochondrial dysfunction stimulates mTORC1, confirmed by a mouse model of adult-onset mitochondrial myopathy complicated by accumulating mtDNA deletions [63]. Interestingly, mTORC1 activation induces cytokines such as FGF21, consistent with the UPR^{mt} through an up-regulation of ATF4 and ATF5, however, the mechanistic details of mTORC1-mediated translational regulation of ATF4 and ATF5 remains elusive [63].

5. Crosstalk between FGF21 and ATF4 in PD

FGF21 has been confirmed as a novel metabolic regulator in non-human primate models. Because of its impressive metabolic benefits and safety profile, FGF21 holds great promise as a drug for diabetes, obesity, and dyslipidaemia. More interestingly, due to its low affinity with heparin, FGF21 can penetrate the BBB via simple diffusion and has a potential protective effect on the brain. FGF21 has been demonstrated to play an important role in brain metabolism, protection, and cognition [64]. One important downstream effector of FGF21 signalling is PPAR-γ. PPAR-γ is a nuclear receptor that is primarily expressed in adipocytes. It acts as a ligand-dependent transcription factor and regulates gene expression responsible for adipocyte growth and differentiation. It plays a critical role in obesity and diabetes due to its ability to increase insulin sensitivity [65]. Many studies have shown that PPAR-γ can protect neurovascular units against ischemic injury by reducing inflammation and oxidative stress, improving angiogenesis, and inhibiting neuron apoptosis [66].

Clinically heterogenous mitochondrial diseases frequently affect the nervous system [67]. High energetic requirement of neurones is what makes it vulnerable to mitochondrial dysfunction. Mutations in the mitochondrial fusion gene OPA1 and the mitochondrial DNA polymerase gene POLG has been known to contribute to PD [68]. Mutations in PINK1 and PARKIN are characteristics of juvenile PD and loss of complex I activity causes loss of DA neurones in the SN mainly observed in sporadic PD. Hence, mitochondrial dysfunction can be vital in the pathogenesis of PD. Specific turnover of mitochondria known as mitophagy are also involved in the pathogenesis of diabetes, PD and insulin resistance condition [69]. Mitochondrial abnormalities relative to structure and function are critically controlled by autophagy [70]. Several studies have showcased the possible connection between induction of FGF21 in a deficient muscle with dysfunctional mitochondria in a ATF4 dependent manner. However, mitochondrial dysfunction in PD go a long way as disturbances in the mitochondrial protein PINK and PARKIN result in oxidative stress, altered mitochondrial dynamics and decrease in complex I proteins [71]. With many candidates failing in clinical trials, targets that could effectively restore mitochondrial dynamics are still under scrutiny. The UPR elicited as a result of mitochondrial stress is mainly due to aggregated or misfolded proteins in the mitochondria. UPR is also found to be cross- regulated with ISR. Phosphorylation of elf2α regulates all the stress signalling pathways of ISR.

Downstream of ISR is the signalling by ATF4. In multicellular organisms, increased expression of the transcription factor ATF4 is a predominant marker of mitochondrial dysfunction [72–78]. Quiros et al. used HeLa cells with four different mitochondrial inhibitors, combined with transcriptomic, proteomic, and metabolomic analysis that resulted in acute pharmacological inhibition of mitochondrial function [72]. This study identified ATF4 as a key regulator of the mitochondrial retrograde response in HeLa cells confirmed by ATF4-binding motif in regulated genes, as well as regulation of known ATF4 targets. In the ATF4 50 untranslated region (UTR), eIF2α controls the ATF4 levels through preferential translation of upstream Open Reading Frames (ORFs) [79]. The ER, UPR and the ISR regulates eIF2α phosphorylation through four independent kinases [80]. In presence of mitochondrial dysfunction, eIF2α inhibition disrupted ATF4 activation and its target genes. However, other branches of the ER UPR remain unaffected by mitochondrial dysfunction and no single ISR kinase was necessary for the upregulation of ATF4 in response to mitochondrial dysfunction. Hence, in this study the proximal mechanism by which mitochondrial dysfunction regulates eIF2α was not established. Activation of eIF2α and increased ATF4 expression was also demonstrated by a related study using HeLa cells, in response to loss of mitochondrial DNA, or inhibition of mitochondrial translation after treatment with doxycycline [77]. In a study conducted on hippocampal HT22 cells for resistance against oxidative glutamate toxicity, the cystine/glutamate antiporter system x_c^-, which imports cystine for synthesis of the antioxidant glutathione, and its specific subunit, xCT, are upregulated mainly via upregulation of ATF4 [81]. Further, xCT is found to inhibit ferritinophagy in triple negative breast cancer cells, via controlling levels of glutathione. Ferritinophagy accounts for PD pathogenesis via the activation of Protein Kinase C alpha (PKCα) and MEK in a RAS-independent manner. However, ATF4 mediated ferritinophagy inhibition in PD is yet to be explored.

Potent systemic effects on cellular metabolism is exerted by FGF21. In primary mitochondrial disease patients, in skeletal muscle and in the serum of animal models with mitochondrial disease, FGF21 serum levels are increased [82–84]. FGF21 transcription is strongly upregulated in cultured myotubes treated with mitochondrial inhibitors, or transgenic mice with impaired mitochondrial function in skeletal muscle, this expression of FGF21 exhibits the pattern of a classic mitochondrial retrograde response gene [54,85,86]. During mitochondrial dysfunction in muscle, FGF21 expression is regulated via two mechanisms, the first involving the ISR via ATF4, and a second through p38 MAPK and direct regulation of ATF2 [54,86]. Additionally, in myotubes, p38 MAPK phosphorylation and FGF21 induction were found to be ROS-dependent upon mitochondrial dysfunction [86].

Interestingly, in neurodegenerative condition like PD, analysis of differentiated DA neurons treated with the mitochondrial toxin 1-methyl-4-phenylpyridinium (MPP+) found that upregulation of ATF4 signalling was the only significantly enriched network [87]. In models of PD with acute inhibition of mitochondrial function using various drugs, activation of the ER, UPR is observed in several types of cultured neurons [87–89]. The retrograde response to mitochondrial dysfunction has also been examined in the intact nervous system. The expression of hundreds of genes was altered after administration of the complex I inhibitors, rotenone or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine into the SN including chemical lesion models of PD [90,91]. The mitochondrial uncoupling agent 2,4-dinitrophenol when treated in mice causes transcriptional alterations in various signalling pathways, including inhibition of mTOR signalling and increased ATF4 expression [92]. Pan-neuronal mitochondrial dysfunction in the Drosophila CNS also leads to altered expression of several hundred genes, some of which are targets of Hypoxia Inducible Factor-1 (HIF-1), indicative of a mitochondrial retrograde response. The progression of PD through disrupted autophagy and its link with FGF21 is represented in the Fig. 2.

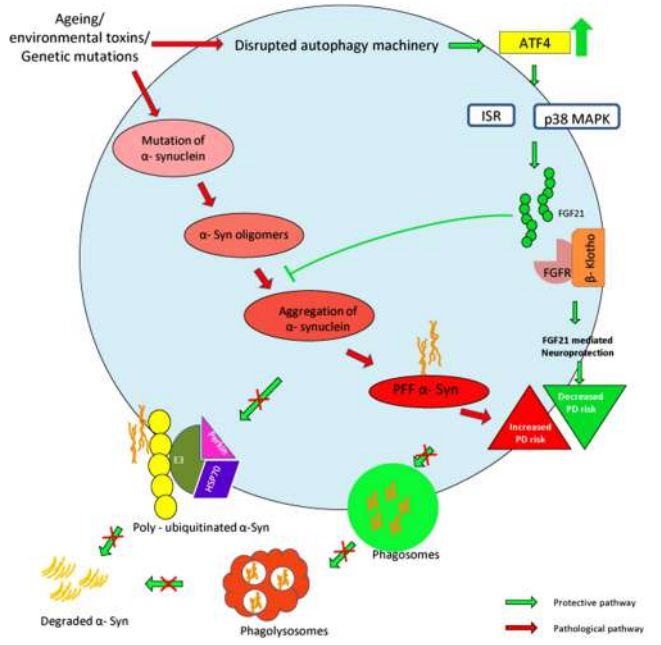

Fig. 2. Link between FGF21 and autophagy: neuroprotective effect of FGF21 possibly via activation of ATF4.

6. Conclusion

Neurodegenerative diseases like PD have taken a toll worldwide as therapies to halt the progression of the disease has cost enormous burden to the society. PD accounts for the second most common neurodegenerative condition, pathologically exerting multiple health anomalies in suffered individuals. Curative approach towards PD is still limited as the exact pathogenesis remains elusive. Despite continued research, the only available symptomatic therapy for PD is a combination of Levodopa and Carbidopa. The fact that the predominant pathology of PD arises due to the accumulation of misfolded proteins, brings autophagy to the limelight. A well-known fact is that autophagy mainly clears unwanted or misfolded proteins maintaining the normal homoeostasis. Autophagy can be of different forms depending on the site of action. However, irrespective of the type, the overall machinery of autophagy tends to slow down with aging and cannot generate the effective mediators required to eliminate the damaged organelles. Surprisingly, autophagy failure increases the expression of several transcription factor acting downstream of autophagy. The expression of these transcription factors in response to aging remains largely unknown. But these transcription factors act in miraculous ways to activate certain neuroprotective factors. A classic example is activation of ATF4 that comes into action upon stress enforced by the ER primarily due to a dysfunctional autophagy. ATF4 is known to upregulate the expression of a widely accepted metabolic hormone FGF21. The antidiabetic, and weight loss effects during obesity exerted by FGF21 is already well established. But recent animal studies have claimed that FGF21 possess strong neuroprotective effects in classic models of AD and PD. Whether FGF21 shows its neuroprotective effect due to dysfunctional autophagy warrants further investigation and remains an attractive area of research with a hope that it can be particularly targeted to halt PD progression.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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