In this review, we summarise the evidence for a role of the ribonuclease angiogenin in the pathophysiology of neurodegenerative disorders, with a specific focus on Parkinson’s disease (PD). Angiogenin is a stress-induced, secreted ribonuclease with both nuclear and cytosolic activities. Loss-of-function mutations in the angiogenin gene (ANG) have been initially discovered in familial cases of amyotrophic lateral sclerosis (ALS), however, variants in ANG have subsequently been identified in PD and Alzheimer’s disease. Delivery of angiogenin protein reduces neurodegeneration and delays disease progression in in vitro and in vivo models of ALS and in vitro models of PD. In the nucleus, angiogenin promotes ribosomal RNA transcription. Under stress conditions, angiogenin also translocates to the cytosol where it cleaves non-coding RNA into RNA fragments, in particular transfer RNAs (tRNAs). Stress-induced tRNA fragments have been proposed to have multiple cellular functions, including inhibition of ribosome biogenesis, inhibition of protein translation and inhibition of apoptosis. We will discuss recent evidence of tRNA fragment accumulation in PD, as well as their potential neuroprotective activities.

**Keywords:** angiogenin; ribonuclease; ribosomal RNA (rRNA); transfer RNA (tRNA); tRNA-derived fragments (tRFs); neuroprotection

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heparan sulfate proteoglycans [16]. It is possible that other angiogenin-binding proteins responsible for angiogenin uptake and signalling will be identified going forward.

REGULATION OF ANGIOGENIN ACTIVITY

The activity of angiogenin is critically regulated by an endogenous inhibitor, ribonuclease/angiogenin inhibitor 1 (RNHI) [24]. Like angiogenin, RNHI is expressed in endothelial cells and many other cell types, including neurons and glial cells [25–27]. RNHI inhibits the activity of angiogenin by binding to its catalytic triad residues Lys-40, His-13 and His-114 [28]. Under stress and anabolic conditions, RNHI accumulates in the nucleus where it binds angiogenin and inhibits tRNA transcription to save energy [29]. Angiogenin activity is therefore a process that is determined by the relative abundance and co-localisation of both proteins in cells.

Similar to other pro-angiogenic factors such as VEGF, transcription of the ANG gene is regulated by the transcription factor hypoxia-inducible factor-1α (HIF-1α). Through this mechanisms, increased HIF-1α expression stimulates angiogenesis in tissues that have insufficient oxygen supply [30]. The hypoxia responsive element within the ANG gene has been mapped to the consensus HIF-1α binding site 5′-RCGTG-3′ [30, 31]. HIF-1α has also been shown to be required for ANG expression in neural cells in response to hypoxia [31]. ANG expression is also positively regulated by the transcription factor hepatic nuclear factor-1α (HNF-1α) [32]. This transcription factor is involved in glucose and lipid metabolism in liver and pancreatic beta-cells.

ANG VARIANTS IN ALS AND PD

Angiogenin became of interest to neuroscience with the initial discovery that ANG gene variants were associated with familial and apparently sporadic cases of ALS in Scottish, Irish, English, Swedish and Northern American families [33]. As part of this study, our laboratory identified that angiogenin is expressed and enriched in motor neurons. Subsequent studies have identified ANG variants in Italian, French, German, Dutch, Belgian, Hungarian, Chinese and Indian ALS patients (Table 1). Several of the ANG variants identified were predicted and subsequently validated to affect angiogenin’s ribonuclease activity due to their proximity to the catalytic site of the protein (Table 2). Other angiogenin variants have been shown to inhibit the shuttling of angiogenin between nucleus and cytoplasm [34], or to reduce the stability of the protein [35]. Subsequent studies showed that angiogenin exerts neuroprotective activities in vitro in models of excitotoxic, hypoxic and trophic factor-withdrawal-induced injury to motor neurons and other neural cells, including dopaminergic SH-SY5Y neuroblastoma cells [31, 36, 37]. Many of the ANG variants identified were shown to have reduced neuroprotective activity compared with wild-type ANG when overexpressed at similar levels in neurons [31, 36]. However, it is currently unknown which cell types in the nervous system (including endothelial cells) are susceptible to ANG mutations.

Of note, subsequent studies also identified ANG variants in familial forms of PD [38, 39]. The two studies identified several non-synonymous ANG variants in Northern American, German, Dutch and Italian PD patients (Table 3). The frequency of PD ANG variants were highly similar in both studies (0.45%/0.47%) compared with controls (0.04%/0%). Furthermore, Van Es et al. reported similar frequency of ALS patients and PD patients carrying ANG variants (0.46%/0.45% compared with 0.04% in controls) [38]. Many of the reported PD ANG variants were predicted to impair angiogenin protein function [38]. In a more recent study, several of these variants were validated to have reduced levels of ribonuclease activity in comparison with wild-type angiogenin [40].

Interestingly, a recent study demonstrated ANG mutations in familial cases of Alzheimer’s disease (AD) [41]. Collectively, these findings point to a general role of angiogenin as a protective factor for central nervous system neurons. Of note, ang1 knock-out mice do not appear to develop

### Table 1. ANG variants associated with ALS

| Variant | Ethnic origin | Reference |
|---------|--------------|-----------|
| M(-24I) | Italian, Hungarian | [69, 70] |
| F(-13L) | German | [71] |
| F(-13S) | Italian | [70] |
| G(-10D) | Dutch | [38] |
| P(-4)S | Italian, Northern American | [34, 70] |
| P(-4)Q | Belgian | [38] |
| Q12L | Irish, Scottish | [33] |
| R31K | Irish, English | [33] |
| K17E | Irish, Swedish | [33] |
| K40I | Irish, Scottish | [33] |
| S28N | Irish, Scottish, North American, French, Dutch, Belgian, German | [33, 34, 38, 71–75] |
| I46V | Scottish, Italian, German, French, Swedish | [33, 38, 70, 71, 76, 77] |
| K54E | German | [71, 75] |
| S28N | North American | [34] |
| P112L | North American | [34] |
| R121H | French | [76] |
| G20G | Italian | [70] |
| V113I | Italian | [70] |
| H114R | Italian | [70] |
| T805 | Dutch | [38] |
| F100I | Dutch | [38] |
| R33W | Hungarian | [69] |
| V103I | Hungarian, Chinese | [69, 78] |
| R145C | Italian | [79] |
| R21G | Indian | [80] |
| C39W | European | [33] |
| g.446C→T | Italian | [70] |

### Table 2. Biochemical characterisation of ribonucleolytic activity of human ALS ANG variants

| Variant | Ribonucleolytic activity % (a) | Reference |
|---------|-------------------------------|-----------|
| K40I | 0.7b | [35, 81] |
| H114R | 1.6b | [40, 81] |
| Q12L | 2.7b | [35, 81] |
| C39W | 4.3b | [35, 81] |
| I46V | 9.3b | [35, 81] |
| K17E | 13.1b | [34, 81] |
| K17E | 19.0b | [35, 81] |
| S28N | 21.1b | [34, 81] |
| P112L | 28.0b | [34, 81] |
| F100I | 39.1 | [40] |
| V103I | 54.1 | [40] |
| R21G | 59 | [80] |

(a)Ribonucleolytic activity of ANG variant towards yeast tRNA in comparison to native ANG (100%)

(b)Reported by [81]
neurodegeneration and ALS-, PD-, or AD-like symptoms or neuropathology in their life span [42], highlighting that aging and/or additional disease processes are required to trigger neurodegeneration. ANG can therefore be added to list of genes that regulate stress responses in neurons and are mutated and contribute to neurodegeneration in various neurological disorders (including PD), as seen in the case of TARDBP mutations, FUS mutations, C9ORF72 repeat expansions, and DJ-1 mutations [43–46].

ANGIOGENIN DELIVERY IS NEUROPROTECTIVE IN MODELS OF ALS AND PD

The ANG mutations that have been reported in ALS and PD patients suggested a direct involvement of angiogenin in pathways leading to motoneuron degeneration or degeneration of dopaminergic neurons. We demonstrated that angiogenin protects cultured primary mouse motor neurons against ALS-associated, stress-induced cell death including excitotoxic injury by promoting and sustaining cell survival signalling through PI3-kinase/Akt kinases [36]. In further preclinical work, we demonstrated that daily, systemic (intraperitoneal) delivery of recombinant human angiogenin protein significantly increased life span and improved motor function in SOD1G93A mice, an established mouse model of ALS [36]. Cell survival signalling in motoneurons was preserved in angiogenin-treated mice. Importantly, the effect of angiogenin, when delivered post-symptom onset (from day 90 onward) on life span and disease progression, was comparable to the effect of a pre-symptom angiogenin treatment (from day 50 onward). These results suggested that angiogenin protein delivery may be beneficial in treating patients with newly diagnosed ALS.

To further validate these findings, our group performed a SOD1G93A mouse model study according to the preclinical guidelines for ALS animal studies set by the 2010 European ALS/MND group [47]. In this study, we demonstrated that systemic delivery of human angiogenin three times per week post-symptom onset (from day 90 onward) delayed motor dysfunction, significantly enhanced survival and protected against motoneuron loss and vascular network regression in the lumbar spinal cord [48].

Angiogenin may also be neuroprotective in PD. Steidinger et al. demonstrated significantly decreased levels of endogenous angiogenin in an alpha-synuclein transgenic mouse model of PD and showed that recombinant human angiogenin protected against dopaminergic neuronal cell death and inhibited caspase-3 activation in neurotoxin-induced in vitro models of PD [49]. A subsequent study by the same group found that virally-mediated overexpression of human angiogenin in the substantia nigra did not protect against dopaminergic cell loss in a neurotoxin-based mouse model of PD [50]. These findings suggest that further in vivo studies are required to explore potential neuroprotective functions in animal models of PD, in particular in genetic models.

Table 3. ANG variants associated with PD

| Variant | Ethnic origin | Reference |
|---------|---------------|-----------|
| M1(-24I) | German | [38] |
| V1(-12A) | Italian | [38] |
| C1(-8D) | Italian | [38] |
| P1(-4S) | Italian, North American, German | [38] |
| H13R | German | [38] |
| K17P* | North American, Dutch, Italian | [38, 39] |
| D22V | Dutch | [38] |
| I46V* | Italian, North American, Dutch, German | [38] |
| K54R | Dutch | [38] |
| R95Q | Dutch | [38] |
| R121C | Italian | [38] |
| K60E | North American | [39] |
| Q77P | North American | [39] |
| A1(-1)P | North American | [39] |

*Variants observed in both PD patients and controls at similar frequency

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TRNA-DERIVED FRAGMENTS (tRFs) AND ‘STRESS-INDUCED TRNA FRAGMENTS’ (tRNAs) IN PD

During stress conditions, angiogenin accumulates in the cytosol where it cleaves non-coding RNAs, including transfer RNAs (tRNAs). Cleavage of tRNAs by angiogenin generates fragments termed ‘stress-induced trna fragments’ or ‘tRNAs’ [12, 51, 52]. Cleavage of tRNAs by angiogenin occurs in their antagonod loop, a process that is highly regulated by tRNA modifications [53–57], so that only specific subsets of tRNA fragments are generated [58]. tRNAs have been shown to inhibit ribosome assembly [12] and to inhibit cap-dependent protein translation via interaction with the initiation factor eIF4F [12]. Both processes may facilitate the recovery of cells during stress conditions, so that resource-consuming or error-sensitive cell functions are stalled during periods of stress. tRNA generation has also been linked to the process of stem cell maintenance and inhibits the proliferation of hematopoietic stem/progenitor cells [42]. Due to their multiple mechanisms of action, lack of tRNA production could be involved in the pathogenic effects of ANG variants in human disease.

tRFs in general are now considered a new class on small non-coding RNAs with multiple cellular functions, of which tRFs are only a subclass. tRFs have been detected in various biological systems suggesting that tRNA cleavage by angiogenin and other ribonucleases is an evolutionary conserved process. Other new functions of tRFs beyond the regulation of protein translation have also been reported. ‘SHOT-tRNAs’, which are analogous to angiogenin-produced tRNAs, were identified in hormone responsive cancer cells where they stimulate their proliferation [59]. Two studies in 2016 showed that tRFs fragments are enriched in sperm cells and delivered to the zygote at fertilization where they modified gene expression by binding to the elements in the zygote’s genome [60, 61]. Multiple ribonucleases other than angiogenin are able to generate such fingerprints, including the ribonucleases Z and Dicer [62–66]. The identification of tRF ‘fingerprints’ in different biological systems and disease conditions is still at its infancy, but interesting observations are now beginning to emerge. A study from our laboratory showed that specific tRFs are associated with epilepsy [67]. Small RNA sequencing analysis of plasma samples collected during video EEG monitoring of patients with focal epilepsy identified significant differences in three specific tRFs fragments compared with healthy controls. Interestingly, these tRFs are different from angiogenin-generated fragments as cleavage did not occur in the anticodon loop. These fragments were elevated in the pre-seizure period, but lower in post-seizure samples, and may represent a novel class of biomarkers indicating seizure risk in epilepsy patients.

A recent study performed in PD patients identified disease-specific tRFs in brain and biofluids [68]. Reanalyses of RNASeq data from three previous studies identified multiple differentially abundant tRFs between PD patients and healthy controls in prefrontal cortex, cerebrospinal fluid and serum. Of note, a subset of the identified tRFs successfully distinguished PD patients from controls with high sensitivity and specificity in each sample collection. Further research is required as to whether these fragments are generated by angiogenin or other ribonucleases. Collectively, these findings suggested that tRF signatures are promising candidates as non-invasive PD biomarkers.
SUMMARY
There is a significant body of evidence suggesting that angiogenin is a stress-induced survival factor for central nervous system neurons. While it has been shown that angiogenin is able to protect against dopaminergic neuron loss in vitro, further research is required to explore its role in animal models of PD. The arrival of new animal models of PD will likely accelerate this translation, as seen in ALS models. Due to its pleiotropic mechanism of action, angiogenin may indeed be an interesting candidate for the treatment of neurodegenerative disorders. It stimulates angiogenin in endothelial cells and promotes neuronal survival through Akt signalling and possibly through the formation of tRNAs, thereby facilitating the recovery of stressed neurons. Moreover, tRFs generated by angiogenin and other ribonucleases may deliver novel diagnostic or prognostic tools for the management of neurodegenerative disorders. Studies are now required to explore the biological functions of these fragments in vitro and in vivo.

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AUTHOR CONTRIBUTIONS
JHMP and EJ wrote the paper.

ADDITIONAL INFORMATION

Competing interests: JHMP is a beneficiary of a patent relating to the use of angiogenin as a diagnostic and therapeutic for ALS and other neurodegenerative disorders. EJ declares no competing interest.

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