Role and therapeutic potential of the pro-longevity factor FOXO and its regulators in neurodegenerative disease

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INTRODUCTION
A major challenge in neurodegenerative disease research is to identify disease-modifying strategies. Given the complexity of sporadic disease such as Alzheimer’s disease (AD) or Parkinson’s disease (PD), the study of inherited neurodegenerative disease is expected to shed light on the mechanisms that underlie neurodegeneration. In this respect, Huntington’s disease (HD), a dominantly inherited disease with CAG expansion in the huntingtin (htt) gene and expanded polyglutamine (polyQ) tracts in the htt protein causing striatal and cortical degeneration (Walker, 2007) has become a “model neurodegenerative disease.” The large number of models for HD, the knowledge on HD mechanisms (Zuccato et al., 2010) and the availability of well-characterized cohorts of HD subjects indeed provide a unique framework in which to investigate the therapeutic potential of target genes and pathways. Among the many genes that could be targeted in HD (Zuccato et al., 2010), longevity modulators, and more largely, genes which are essential to cellular homeostasis are the subject of intense research because they may directly regulate important cell survival mechanisms such as for example oxidative stress response and protein quality control. While several genes may modulate survival mechanisms such as for example oxidative stress response and protein quality control. While several genes may modulate survival mechanisms such as for example oxidative stress response and protein quality control.

THE FOXO NETWORK
Several signaling pathways such as the PI3K–AKT pathway, stress-activated pathways such as the MST-1 and JNK pathways, and the SIR-2 and AMPK pathways converge onto FOXO proteins to regulate a variety of biological processes which are important to development, metabolism, tumor suppression, and longevity (Calnan and Brunet, 2008). A large number of studies have indicated that, in response to external stimuli including growth factors such as insulin and insulin-like growth factor (IGF-1), nutrients, cytokines, and oxidative stress stimuli, these pathways are able to regulate the subcellular localization, DNA binding activity, transcriptional activity, and stability of these FOXO proteins. These studies have been thoroughly reviewed in excellent articles to which we refer for more details (Greer and Brunet, 2005; Calnan and Brunet, 2008; Landis and Murphy, 2010; Yen et al., 2011); a finely tuned regulatory network is emphasized in which, through a series of context-dependent post-translational modifications and interactions with co-regulators, FOXO proteins are able to integrate several types of external stimuli to regulate gene expression and modulate cell cycle arrest, apoptosis, autophagy, angiogenesis, differentiation, stress resistance, stem cell maintenance, glucogenesis, and food intake. Nutrient-sensing pathways are important upstream components of this regulatory network. Nutrient-sensing factors such as insulin/insulin-like growth factor (IGF) signaling (IIS), NAD+–dependent histone deacetylases (sirtuins/SIR-2/SIRTs), the target of rapamycin (TOR) kinase, and ribosomal S6 Kinase (TOR/S6K) pathway and the AMPK pathway may be targeted by dietary restriction to slow aging (Cabreiro and Gems, 2010; Chiachiera and Simone, 2010). Additionally, nutrient-sensing pathways are also key regulators of FOXO activity.

Studies in simple model organisms have yielded crucial insights into the genetic and molecular aspects of longevity. FOXO, which is most notable for its association with longevity, and its upstream regulators such as sirtuins have received particular attention in translational research because these genes modulate cell survival in several models of neurodegenerative diseases. There is a large amount of knowledge on the pathways that regulate FOXO activity and genes that may be regulated by FOXO. However, for the same reason that the FOXO network is a complex stress response system, its therapeutic potential to develop disease-modifying strategies requires further examination. Although the FOXO network contains druggable genes such as sirtuins and AMPK, whether they should be activated or inhibited and whether protection against the early or late phases of neuronal cell decline might require opposite therapeutic strategies remains unclear. Additionally, the mode of action of small compound molecules believed to act on FOXO network targets was questioned. This review recapitulates essential facts and questions about the promises of FOXO and its interactors in neurodegenerative disease.

Keywords: Foxo, longevity, disease
It is for example well-established that IIS modifies FOXO proteins at specific phosphorylation sites, with reduction of IIS activating FOXO, which may translate into lifespan extension in invertebrates (Calnan and Brunet, 2008). Besides IIS and modulation of FOXO phosphorylation, the SIRT1 nutrient-sensing pathway and modulation of FOXO acetylation is another important FOXO regulator. Increased sir-2.1/ SIRT1 dosage in high-copy sir-2.1 transgene containing strains was indeed found to strongly increase lifespan in C. elegans, an effect that requires daf-16/FOXO (Tissenbaum and Guarente, 2001), suggesting that sirtuins could play important roles in lifespan extension. This notion has been recently challenged by additional studies in C. elegans and Drosophila melanogaster (Burnett et al., 2011; Rizki et al., 2011). These studies revealed that lifespan extension may be partially attributable to background mutations producing a dye-filling defective (“Dfy”) phenotype in high-copy sir-2.1 overexpressor strains (Burnett et al., 2011; Rizki et al., 2011). While this raised the possibility that sirtuins might not be longevity-promoting factors to that extent, two independent studies indicated that lifespan extension (10–15%) may also be achieved in low-copy sir-2.1 mutant backgrounds (Berdichevsky et al., 2006). Furthermore, background mutations were not responsible for the strong level of neuroprotection against mutant polyQs by sir-2.1 overexpression (Burnett et al., 2011). Thus, while additional investigation will be needed to determine to which extent sirtuins may promote lifespan extension, sirtuins stand as important longevity factors that are relevant to neuronal protection in neurodegenerative disease and other protective effects in metabolic disease (Kim et al., 2007; Baur et al., 2010; Burgess, 2011; Jeong et al., 2011; Jiang et al., 2011). One may wonder why mutations producing a Dfy phenotype were found in sir-2.1 overexpressor strains despite the care made by the C. elegans community with distributing mutants after multiple outcrosses. The answer might come from studies made with the search for mutants resistant to avermectin (Rand and Johnson, 1995), an antiparasitic drug. Many low-level ivermectin resistance mutations in che, osm, and dyf genes may produce defects in the amphid sensilla, low-level ivermectin resistance is common in C. elegans (1 in 5000 eggs in the absence of mutagenesis) and the ivermectin resistance allele frequency in wild nematode populations may be as high as 1% (C. D. Johnson, personal communication). Additionally, mutations that cause defects in sensory cilia genes may also extend longevity (Apfeld and Kenyon, 1999). The dyf mutations may thus occur at relatively high rates, which calls for the regular assessment of C. elegans mutants for dye-filling defects in studies of longevity.

In addition to be regulated by kinases and deacetylases, FOXO activity is regulated by ubiquitin complex members such as Skp2, a protein that promotes FOXO1 degradation (Huang et al., 2005), and by co-factors such as β-catenin, a protein that binds to FOXO3a and regulates its transcriptional activity in response to oxidative stress (Eisers et al., 2005). The FOXO proteins may compete with the canonical Wnt effector T cell factor (TCF) for binding to β-catenin (Hoogeboom et al., 2008), which further highlighted the importance of β-catenin in the regulation of FOXO activity. While FOXO proteins may act together with other transcription factors to regulate gene expression (Landis and Murphy, 2010), they stand at the center of a large network of upstream regulators, co-factors, and downstream targets (Figure 1) which are important for cell homeostasis. Interestingly, studies based on chromatin immunoprecipitation (Oh et al., 2006; Schuster et al., 2010), gene expression profiling in C. elegans (McElwee et al., 2003; Murphy et al., 2003) and mouse neural stem cells (NSCs; Paik et al., 2009; Renault et al., 2009), and other approaches (Lee et al., 2003; Yu et al., 2008) highlighted thousands of putative FOXO-regulated genes (Jensen et al., 2006; Murphy, 2006). These results open the avenue to a better understanding of FOXO activity in regulating downstream mechanisms in specific contexts. Given that FOXO proteins act in specific cells and tissues to execute different outputs (Landis and Murphy, 2010), it is anticipated that specific transcriptional targets may be engaged into different FOXO-mediated responses. Gene expression studies performed in either C. elegans nematodes (McElwee et al., 2003; Murphy et al., 2003) or mouse NSCs (Lee et al., 2003; Yu et al., 2008) emphasized a small number of FOXO-regulated genes across species and biological conditions (Table 1). Although poor overlap may be partially attributable to differences in the species and/or methods used for gene expression profiling, these studies suggest that FOXO proteins indeed regulate specific targets in different contexts. In addition to being important for stem cell homeostasis and adult longevity, FOXO factors are involved in development and cell differentiation (Kitamura et al., 2007; Demontis and Perrimon, 2009; Yuan et al., 2009; de la Torre-Ubieta et al., 2010; Kerdiles et al., 2010; Schuff et al., 2010), and they may be important to promote adult neurogenesis as suggested by studies in Drosophila melanogaster (Siegrist et al., 2010). Thus, FOXO factors may be essential to cell response homeostasis during the entire lifetime of a living organism. As such, it is not surprising that FOXO proteins and their main regulators such as sirtuins were implicated in the protection against age-associated diseases such as cancer, diabetes, cardiovascular disease, and neurodegeneration (Dansen and Burgering, 2008; Chiachiera and Simone, 2010; Herranz and Serrano, 2010).

**THE SIR-2/FOXO PATHWAY AND ITS ROLE IN DEGENERATIVE DISEASE**

For the same reason that pathways converging onto FOXO are important to cell survival and longevity, they are of particular interest to explore how to promote neuron or muscle cell survival in degenerative disease. Over the past years, accumulating evidence on the therapeutic potential of FOXO and its interactors for age-related diseases has been obtained. Perhaps the first observation suggesting that longevity-promoting factors might be able to modulate the toxicity of degenerative disease proteins was obtained in the nematode C. elegans. In transgenic nematodes expressing polyQ tracts in body wall muscle cells, reducing IIS by use of age-1/Pi3K loss-of-function (LOF) mutants decreased the toxicity associated to expanded polyQs, and this effect was dependent on daf-16/FOXO (Morley et al., 2002). Direct evidence for longevity-promoting factors such as SIR-2 and FOXO to protect diseased neurons at an early stage of cellular decline was obtained by using a C. elegans model of HD pathogenesis.
Table 1 | Putative FOXO targets emphasized by microarray analysis in either *C. elegans* or mouse NSCs, or both.

| Mouse gene name | Worm ORF ID | *C. elegans* | *Mouse NSCs* |
|-----------------|-------------|--------------|--------------|
|                 |             | Murphy et al. (2003) | McElwee et al. (2003)* | Renault et al. (2009) | Paik et al. (2009) |
| Cav-1           | T13F2.8     | U            | –            | D             | –              |
| Mxd-1           | R03E9.1     | D            | –            | D             | D              |
| Soc-2           | C08A8.1     | D            | U            | –             | –              |
| Crisp           | F49E11.9, H10D18.2, ZK384.1, ZK384.2 | D | U (F49E11.9) | – | – |
| RIKEN cDNA 6230409E13 | C54D10.1   | D            | U            | –             | –              |
| Nxi-1           | F17B6.1     | D            | U            | –             | –              |
| Dgc-1           | K07B1.4     | D            | U            | –             | –              |
| Birc-5          | C50B8.2     | –            | U            | –             | U              |
| Myo-1b          | F28D10.4    | –            | U            | –             | U              |
| Slic-25a6       | W02D3.6     | –            | U            | –             | U              |
| B3gait1         | E03H4.11    | U            | –            | –             | U              |
| Chna-7          | R02E12.8    | U            | –            | –             | U              |
| Gmeb-1          | C44F1.2     | U            | –            | –             | U              |
| Gsp-1t          | H19K07.1    | U            | –            | –             | U              |
| Jsg-1           | R107B       | U            | –            | –             | –              |
| Lta-4h          | ZC416.6     | U            | –            | –             | U              |
| Mapk-8          | B047B.1     | U            | –            | –             | U              |
| Pcn-1           | W03D0.24    | U            | –            | –             | U              |
| Psmc-5          | Y49E10.1    | U            | –            | –             | U              |
| Bph-l           | K01A2.5     | U            | –            | –             | D              |
| Dpy-3           | C25F6.3     | U            | –            | –             | D              |
| S1c-15a-2       | K04E72      | U            | –            | –             | D              |
| Comt-1d         | Y40B10A.2, Y40B10A.6 | D | – | – | U |
| Gnb-5           | F52A8.2     | D            | –            | –             | U              |
| Icmt            | F21F3.3     | D            | –            | –             | U              |
| Rexo-1          | Y58A3A.33   | D            | –            | –             | U              |
| Abhd-4          | C37H5.2     | D            | –            | –             | D              |
| Acsl-3          | C46F4.2     | D            | –            | –             | D              |
| Alkbh-4         | F09F77      | D            | –            | –             | D              |
| Cat             | Y54G11A.6   | D            | –            | –             | D              |
| Cyb-5           | W02D3.1     | D            | –            | –             | D              |
| Fads-2          | W06D2.4     | D            | –            | –             | D              |
| Ppap-2c         | T26D9.3     | D            | –            | –             | D              |
| Syl-11          | T23H2.2     | D            | –            | –             | D              |

U, up-regulated; D, down-regulated. *The promoter of these dysregulated genes also contain FOXO binding sites (McElwee et al., 2003). –, Not dysregulated. This table is based on the simple comparison of four studies performed in either *C. elegans* (McElwee et al., 2003; Murphy et al., 2003) or mouse NSCs (Lee et al., 2003; Yu et al., 2008).

in which expression of polyQ-expanded N-terminal huntingtin in touch receptor neurons induced neuronal dysfunction (loss of response to light touch) in the absence of cell death (Parker et al., 2001). In these animals, increased *sir-2.1*/SIRT1 dosage protects from expanded polyQs, with reduction of axonal dystrophy, whereas *sir-2.1* LOF aggravates expanded polyQ toxicity (Parker et al., 2005). This neuroprotective effect is not due to unrelated mutations (i.e., mutations producing a Dyf phenotype) in the high-copy *sir-2.1* transgene containing strains as neuroprotection was observed to the same extent in non-Dyf, *sir-2.1* overexpressors (Burnett et al., 2011). Additionally, *sir-2.1* neuroprotection in this model requires *daf-16*/FOXO (Parker et al., 2005), emphasizing a role for the SIR-2.1/DAF-16 pathway. This suggested that raising the activity of the SIRT1 pathway may protect from mutant huntingtin in mammalian models of HD. This notion was supported by other *C. elegans*-based studies (Bates et al., 2006), and consistent with the protective effects of sirtuins in common neurological disorders. However, studies in *Drosophila melanogaster* suggested that Sir-2 knockdown protects from neurodegeneration as induced by N-terminal htt expression in the compound eye, with no effect of overexpressing Sir-2 (Pallos et al., 2008). These results suggested that the role of Sir-2 in
FIGURE 1 | Simplified view of the FOXO network. This diagram shows signaling pathways well-established (straight arrows) or hypothesized (dashed arrow) to converge onto FOXO. The list of target gene classes and physiological outputs is not exhaustive.

mutant polyglutamine neurons may be complex. Nematodes with expanded polyQ expression in touch receptor neurons recapitulate neuron dysfunction before cell death and pointed to the FOXO-dependent effect of homozygous loss of Sir-2 (Parker et al., 2005). Flies with expanded polyQ expression in the eye show neurodegeneration and pointed to an effect of heterozygous loss of Sir-2 that may be unrelated to longevity (Pallos et al., 2008). While these differences illustrated the importance of parameters such as the severity of pathology, type of gene dosage and identity of downstream effectors when pursuing therapeutic targets, two independent studies recently reported that SIRT1 is neuroprotective in several mouse models of HD (Jeong et al., 2011), providing evidence for SIRT1 to protect diseased neurons. Neurite outgrowth, cell viability and tolerance to degeneration induced by Aβ(1–42) oligomers are promoted in primary neurons from mice with neuron-specific SIRT1 overexpression (Guo et al., 2011), further supporting the notion that SIRT1 is able to protect diseased neurons. In C. elegans nematodes expressing Aβ(1–42) in body wall muscle cells (Link et al., 2003), daf-16/FOXO and heat shock factor 1 (hsf-1) cooperate to regulate a two-step cell survival response involving disaggregation/aggregation (Cohen et al., 2006). Consistently, in a mouse model of AD (APPsw/Presenilin1-ΔE9 mice), genetically reducing IGF signaling protects from Alzheimer’s-like disease symptoms (Cohen et al., 2009). Finally, it is notable that allelic variation in FOXO3A was associated with the ability to be long-lived as suggested by several association studies in populations of centenarians (Willcox et al., 2008; Anselmi et al., 2009; Flachsbart et al., 2009; Li et al., 2009; Soerensen et al., 2010; Kleinordt et al., 2011).

While the SIR-2.1/DAF-16 pathway may protect mutant polyQ neurons, it has opposite effects in a C. elegans model of oculopharyngeal muscular dystrophy (OPMD), a late-onset disease caused by expanded polyalanines in the PABPN1 protein (Catoire et al., 2008). In C. elegans transgenics expressing human PABPN1 in body wall muscle cells, sir-2.1 overexpression indeed aggravates muscle cell decline and abnormal motility caused by mutant PABPN1 expression, whereas sir-2.1 LOF is protective in a daf-16/FOXO-dependent manner (Catoire et al., 2008). These observations suggested that the status of FOXO activity in mutant polyQ neurons is different from that of mutant polyAla muscle cells. These results also suggested that SIRT1 inhibitors have therapeutic potential in OPMD as further illustrated by pharmacological studies in PABPN1 nematodes (Pasco et al., 2010).

MODULATION OF NEURODEGENERATIVE DISEASE TARGETS IN THE FOXO NETWORK

Over the past years, studies of SIRT1/FOXO activity in models of disease have the search for SIRT1 activators and inhibitors with clinical potential. While the aim of this review is not to cover drug discovery and clinical development in the field of sirtuin research, it is notable that the mechanisms of action of SIRT1-activating compounds (STACs) have been the subject of debate. This applies to resveratrol, a plant polyphenol that has a broad range of beneficial activities on health span (Wood et al., 2004; Baur et al., 2006; Fulda and Debatin, 2006; Lagouge et al., 2006), is neuroprotective in several models of neurodegenerative diseases (Parker et al., 2005; Kim et al., 2007; Bizat et al., 2010; Richard et al., 2011) and has attracted a lot of attention as a potential drug (Patel et al., 2011). Resveratrol was initially thought to primarily activate SIRT1 (Howitz et al., 2003). It is now thought that resveratrol has multiple mechanisms of action
enzymes \( (Wang \ et \ al., \ 2007, \ 2011; \ Li \ et \ al., \ 2008; \ Zhao \ et \ al., \ 2010) \) as HD \( (Zuccato \ et \ al., \ 2010) \), it is tempting to speculate that drial and metabolic defects in neurodegenerative diseases such as cancer-specific metabolism \( (Chiacchiera \ and \ Simone, \ 2009, \ 2010; \ Chiacchiera \ et \ al., \ 2009) \), raising the possibility that AMPK–FOXO might contribute to neurodegeneration, which might be particularly harmful during the late phases of the pathogenic process in neurodegenerative disease. Studies in models of neurodegeneration reflect the complexity of the AMPK-mediated regulation of cell survival. Although the AMPK activator metformin protects primary cortical neurons from etoposide-induced cell death \( (El-Mir \ et \ al., \ 2008) \) and ameliorates survival and motor defects in R6/2 transgenic mice expressing mutant N-terminal huntingtin \( (Ma \ et \ al., \ 2007) \), other studies suggested that metformin may increase the generation of Aβ peptides via BACE1 upregulation in cellular models \( (Chen \ et \ al., \ 2009) \). In regard to AMPK activity in neurons, conflicting observations have been made. Because neurons do not efficiently store nutrients, AMPK might be essential to neuron activity and survival, suggesting that AMPK activation might protect neurons from metabolic stress in neurodegenerative disease. However, AMPK appears to be abnormally activated in pre-tangle and tangle neurons in AD and other tauopathies \( (Vingtdeux \ et \ al., \ 2011) \). Additionally, there is nuclear translocation of the AMPK-alpha1 subunit in the striatum of post-mortem HD brains and mice with a fast-developing HD pathology \( (Ju \ et \ al., \ 2011) \). While this suggests that AMPK might have a pathological role in HD, studies of AMPK in additional models of HD are warranted considering the pro-survival role of AMPK in neurons and diversity of pathology in HD mice. Collectively, these data highlight the need for more studies of the modulation of AMPK activity toward specific targets in models that recapitulate the early/mild versus late/severe components of the pathogenic process in neurodegenerative disease. This will allow the potential of AMPK-targeted therapy in neurodegenerative disease treatment to be clarified. It will also be important to identify the small compound molecules that might be used in this respect \( (Steinberg \ and \ Kemp, \ 2009) \).

**PERSPECTIVES**

There is accumulating evidence on the protective role of FOXO proteins and their interactors in response to cellular stress in age-related diseases. One of the current challenges is to identify the downstream mechanisms by which FOXO factors are essential to neuron survival in neurodegenerative disease. Given the complex regulation of gene expression by FOXO proteins and their interactors, it will be important to investigate how FOXO transcriptional targets may be involved in the regulation of survival responses in specific neurodegenerative diseases and to evaluate whether this may be relevant to other neurodegenerative diseases. Another challenge is to assess whether the pathways that regulate FOXO transcriptional activity should be activated or inhibited to modify the pathogenic process in neurodegenerative disease, and whether the same approach should be used against the early/mild versus late/severe phases of the pathology. Sustaining neuron survival at an early phase of the pathology and reducing neuronal cell death in late disease might require the same FOXO activity to be modulated in opposing fashions. This possibility is supported by the ability of FOXO proteins and their interactors to orchestrate two-step responses in which the net outcome may be cell survival \( (Cohen \ et \ al., \ 2006) \) or cell demise \( (Chiacchiera \ and \ Simone, \ 2009) \).
2010) in response to prolonged stress. Thus, while several questions remain unanswered, future and exciting developments are expected to shed light on the importance and therapeutic potential of FOXO protein targets in neurodegenerative disease.

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