HHS Public Access

Author manuscript

Curr Neurovasc Res. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

Curr Neurovasc Res. 2017 ; 14(4): 415–420. doi:10.2174/1567202614666171116102911.

Forkhead Transcription Factors: Formulating a FOXO Target for Cognitive Loss

Kenneth Maiese[*,1]

[1]Cellular and Molecular Signaling, Newark, New Jersey 07101

Abstract

BACKGROUND—With almost 47 million individuals worldwide suffering from some aspect of dementia, it is clear that cognitive loss impacts a significant proportion of the global population. Unfortunately, definitive treatments to resolve or prevent the onset of cognitive loss are limited. In most cases such care is currently non-existent prompting the need for novel treatment strategies.

METHODS—Mammalian forkhead transcription factors of the O class (FoxO) are one such avenue of investigation that offer an exciting potential to bring new treatments forward for disorders that involve cognitive loss. Here we examine the background, structure, expression, and function of FoxO transcription factors and their role in cognitive loss, programmed cell death in the nervous system with apoptosis and autophagy, and areas to target FoxOs for dementia and specific disorders such as Alzheimer's disease.

RESULTS—FoxO proteins work in concert with a number of other cell survival pathways that involve growth factors, such as erythropoietin and neurotrophins, silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1), Wnt1 inducible signaling pathway protein 1 (WISP1), Wnt signaling, and cancer-related pathways. FoxO transcription factors oversee pro-inflammatory pathways, affect nervous system amyloid (Aβ) production and toxicity, lead to mitochondrial dysfunction, foster neuronal apoptotic cell death, and accelerate the progression of degenerative disease. However, under some scenarios such as those involving autophagy, FoxOs also can offer protection in the nervous system and reduce toxic intracellular protein accumulations and potentially limit Aβ toxicity.

CONCLUSIONS—Given the ability of FoxOs to not only promote apoptotic cell death in the nervous system, but also through the induction of autophagy offer protection against degenerative disease that can lead to dementia, a fine balance in the activity of FoxOs may be required to target cognitive loss in individuals. Future work should yield exciting new prospects for FoxO proteins as new targets to treat the onset and progression of cognitive loss and dementia.

Keywords

aging; aging-related disorders; Alzheimer's disease; apoptosis; autophagy; cell longevity; deoxyribonucleic acid; diabetes mellitus; erythropoietin; forkhead transcription factors; FoxO; growth factors; erythropoietin; Huntington's disease; metabolism; mitochondria; oxidative stress; programmed cell death; silent mating type information regulation 2 homolog 1 (*Saccharomyces*

[*]**Correspondence to:** Kenneth Maiese, MD, Cellular and Molecular Signaling, USA. wntin75@yahoo.com.

Competing Interests: There are no conflicts of interest to declare.

cerevisiae) (SIRT1); sirtuin; wingless; Wnt1 inducible signaling pathway protein 1 (WISP1); Wnt signaling

The Impact of Cognitive Loss in the Global Population

Nervous system disorders affect a significant proportion of the world's population and result in disability and death for multiple individuals. In particular, cognitive disorders such as Alzheimer's disease (AD) can impact greater than 5 million individuals in the United States. Familial cases of AD account for less than 2% of all presentations of AD (1, 2). Throughout the world, almost 47 million people suffer from some form of dementia with approximately 60% of these cases resulting from AD (2–5). Unfortunately, the availability of definitive treatments to resolve or prevent the onset of cognitive loss are limited and to the most extent are non-existent (6, 7). For example, alternative treatments provide only some relief to limit the progression of symptoms (8–13). As a result, it is vital to explore novel strategies that can potentially target, treat, and possibly limit the onset and progression of cognitive loss in patients suffering from such disorders.

FoxO and the Family of Forkhead Transcription Factors

Mammalian forkhead transcription factors may be one such avenue that can offer effective therapeutic strategies for dementia and cognitive loss (14–17). Greater than one hundred forkhead genes and 19 human subgroups that range from *FOXA* to *FOXS* are known to exist since the original discovery of the *Drosophila melanogaster gene forkhead* (18). If one focuses upon the mammalian FOXO proteins of the O class, these forkhead box class transcription factors have the members FOXO1, FOXO3, FOXO4, and FOXO6 (19). Previous terminology for forkhead proteins included forkhead in rhabdomyosarcoma (FKHR) (FOXO1), FKHRL1 (forkhead in rhabdomyosarcoma like protein 1) (FOXO3a), the Drosophila gene fork head (*fkh*), Forkhead RElated ACtivator (FREAC)-1 and -2, and the acute leukemia fusion gene located in chromosome X (*AFX*) (*FOXO4*) (20, 21). With the current nomenclature, an Arabic number is provided with the designation of "Fox", then a subclass or subgroup letter is provided, and finally the member number is listed within the subclasses of the Fox proteins (22). All letters are capitalized for human Fox proteins. For the mouse, only the initial letter is listed as uppercase and for all other chordates the initial and subclass letters are in uppercase (23–25).

FoxO proteins are transcription factors and bind to deoxyribonucleic acid (DNA) through the FoxO-recognized element in the C-terminal basic region of the forkhead DNA binding domain (26, 27). Following forkhead binding to DNA, target gene expression is repressed or activated through fourteen protein-DNA contacts with the primary recognition site located at α-helix H3 (28). Phosphorylation or acetylation that can block FoxO activity may alter the binding of the C-terminal basic region to DNA to prevent transcriptional activity (29). In addition, multiple mechanisms may contribute to forkhead DNA binding that involve variations in the N-terminal region of the recognition helix, changes in electrostatic distribution, and nuclear translocation of FoxO proteins (30–33).

FoxO Transcription Factors in the Nervous System

FoxO proteins are expressed in all tissues of the body, but serve to have multiple roles in the nervous system (27, 34). Interestingly, individual FoxO proteins can have selective expression in the nervous system (27, 34). For example, FoxO6 is present in several regions of the brain, such as the hippocampus, the amygdala, and the nucleus accumbens (35, 36) and may control memory consolidation and emotion (37). FoxO6 also is involved in other regions of the body and may control hepatic gluconeogenesis and cellular metabolism (38). FoxO3 may be involved in a number of pathways that involve in auditory synaptic transmission (39), cerebral endothelial vascular cell survival (40, 41), oxidative stress injury in mouse cerebellar granule neurons (42), erythroid cell growth (43), hippocampal neuronal injury (44, 45), and neonatal hypoxic-ischemic encephalopathy (46). In relation to FoxO1, this transcription factor may impact astrocyte survival (47), embryonic endothelial stem cell survival (48), ischemic brain injury (49), vascular disease (50), and memory pathways in the striatum and sub-regions of the hippocampus (35).

FoxO Transcription Factors and Cell Death

FoxO transcription factors may impact cognitive loss through the modulation of pathways that involve programmed cell death pathways of autophagy and apoptosis (51, 52). In regards to autophagy, FoxO proteins may be protective. Some studies suggest that FoxO activity, such as FoxO1, can function to increase basal autophagy and reduce atherogenesis (53, 54). Ectopic expression of FoxO1 enhances autophagy and toxic mHtt protein clearance in neuronal cell cultures (55). In addition, a loss of FoxO activity with autophagy inhibition during aging may contribute to neuronal dysfunction and the induction of β-amyloid (Aβ) production (56).

In regards to apoptosis, loss of FoxO activity usually improves cell survival. Loss of FoxO transcription factors can protect against microglial cell demise during oxidative stress (57) and Aβ exposure (58), promotes the protective effects of metabotropic glutamate receptors (59), increases neuronal cell survival through nicotinamide adenine dinucleotide (NAD^+) precursors (60), enhances survival with growth factors (61), such as erythropoietin (EPO) (30, 40, 43, 62) and neurotrophins (63–65), and can lessen metabolic and vascular disease (66). Work has suggested that some antipsychotics, such as clozapine, may function through FoxO inhibition to protect against apoptotic neuronal cell loss (67).

In some scenarios, pathways involving silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1) and Wnt signaling may affect FoxO modulation of apoptotic cell death. In cortical bone formation, loss of SIRT1 activity can lead to depletion of Wnt activity with a corresponding increase in FoxO activity and the loss of bone formation (68). SIRT1 can result in enhanced neuronal survival through modulation of FoxO activity (69–73). SIRT1-mediated deacetylation of FoxO1 also results in starvation-induced increases in autophagic flux that can maintain vascular and cardiac left ventricular function during periods of starvation (74). Under some conditions, sirtuins and FoxO transcription factors may function synergistically to increase neuronal cell survival (4, 71). FoxO proteins in conjunction with SIRT1 pathways may offer protection against Aβ toxicity (75) and

forkhead transcription factors, such as FoxO3a, may be dependent upon SIRT1 to reduce oxidative stress and cell injury during exposure to Aβ (76). In models of Drosophila, loss of FoxO and SIRT1 activity with a reduction in autophagy activity can lead to neuronal accumulation of Aβ (56).

In addition, Wnt signaling pathways (77) with Wnt1 in microglial cells of the central nervous system can block apoptosis through the post-translational phosphorylation and sequestration of FoxO3a in the cytoplasm to prevent caspase activation (78). Wnt1 inducible signaling pathway protein 1 (WISP1), a target of Wnt signaling (79, 80), prevents apoptotic neuronal death through the post-translational phosphorylation of FoxO3a, sequestration of FoxO3a in the cytoplasm with protein 14-3-3, and limiting the deacytelation of FoxO3a (44). Neuroprotective trophic factors and cytokines, such as EPO (22, 30, 40), rely upon Wnt signaling to offer cellular protection through the inhibition of FoxO proteins.

FoxO Transcription Factors and Cognitive Loss

FoxO transcription factors can affect multiple pathways in the body and influence a number of disease entities (34, 81). As an example, FoxO proteins are considered as therapeutic targets for cancer (23, 82–84), diabetes mellitus (30, 85, 86), and pathways involving oxidative stress (82, 87, 88). Interestingly, FoxO transcription factors also play a significant role in inflammation. The FoxO pathway can affect renal inflammation (89), vascular inflammatory pathways (21), and cardiac injury (21).

Some of these very same pathways involving FoxOs including cancer-related signaling pathways (90, 91) also impact the nervous system and cognition. Calcineurin and FoxO3 can interact in astrocytes during Aβ exposure that results in pro-inflammatory cytokines and injury to neurons (92). FoxO transcription factors could be considered a target to block Aβ production and possibly suppress the onset and progression of AD. Nuclear translocation of FoxO3 is tied to apoptotic neuronal DNA damage (15, 45, 93). Histone deacetylase 2 (HDAC2) can form a physical complex with FoxO3a that can lead to oxidative stress-induced cerebellar granule neuron apoptosis (42). In some circumstances, Aβ can result in the dephosphorylation and mitochondrial translocation of FoxO3a that leads to mitochondrial dysfunction (17). Blockade of FoxO activity can protect against oxidative stress and Aβ toxicity (58, 94). Increased FoxO activity can function in concert with tribbles pseudokinase 3 to result in apoptotic and autophagic Aβ induced neuronal cell death (95).

Yet, as previously noted, some studies suggest that Aβ toxicity may be attenuated through SIRT1 and FoxO3a antioxidant dependent pathways (76) as well as those involving autophagy. In models of full-length mutant Huntingtin (mHtt) transgenic mice, ectopic expression of FoxO1 enhances autophagy and toxic mHtt protein clearance in neuronal cell cultures (55). SIRT1 and FoxO proteins can function synergistically to promote cell survival. As an example, in differentiated chrondrocytes exposed to oxidative stress, forkhead transcription factors FoxO1 and FoxO3 in combination with SIRT1 activity are protective with the production of autophagic related proteins (87). In other systems such as the maternal decidua, FoxO proteins may function independently during oxidative stress with

FOXO1 preventing oxidative stress damage and FOXO3a promoting oxidative cell death (96).

Considerations for the Future

Cognitive disorders affect a significant proportion of the world's population. Yet, the availability of treatments that can resolve the loss of cognition are severely limited. Mammalian forkhead transcriptions of the O class (FoxOs) offer an exciting pathway to develop novel treatments for cognitive loss. These transcription factors can target gene expression in the nervous system and are found in regions that affect memory, such as the hippocampus. FoxOs oversee the programmed cell death pathways of autophagy and apoptosis. Under some scenarios such as with autophagy, FoxOs can offer protection in the nervous system and reduce toxic intracellular protein accumulations and potentially limit Aβ toxicity. FoxOs have been shown to reduce oxidative stress and protect neurons through the induction of autophagy. Yet, FoxOs also contribute to apoptotic cellular death and therefore by limiting the activity of FoxOs, neuronal protection can ensue when apoptotic cellular death is prominent. Recent work suggests that some antipsychotics, such as clozapine, may function through FoxO inhibition to protect against apoptotic neuronal cell loss. Importantly, FoxOs function with a number of other cell survival pathways that involve growth factors, such as EPO and neurotrophins, SIRT1, WISP1, Wnt signaling, and cancer-related pathways. Ultimately, FoxOs can lead to the activation of pro-inflammatory pathways, alter Aβ production, result in mitochondrial dysfunction, foster neuronal injury, and accelerate the progression of degenerative Aβ toxicity. Yet, as suggested above, a fine balance that oversees the activity of FoxOs may be required to offset cognitive loss since under some circumstances FoxOs can be protective. Future studies of FoxO transcription factors can provide exciting areas of investigation and discovery to uncover some of the hidden opportunities for new drug development to treat cognitive loss.

Acknowledgments

This research was supported by the following grants to Kenneth Maiese: American Diabetes Association, American Heart Association, NIH NIEHS, NIH NIA, NIH NINDS, and NIH ARRA.

References

1. Filley CM, Rollins YD, Anderson CA, Arciniegas DB, Howard KL, Murrell JR, et al. The genetics of very early onset Alzheimer disease. Cognitive and behavioral neurology : official journal of the Society for Behavioral and Cognitive Neurology. 2007; 20(3):149–56. [PubMed: 17846513]
2. Maiese K. Taking aim at Alzheimer's disease through the mammalian target of rapamycin. Ann Med. 2014; 46(8):587–96. [PubMed: 25105207]
3. Chong ZZ, Li F, Maiese K. Oxidative stress in the brain: Novel cellular targets that govern survival during neurodegenerative disease. Prog Neurobiol. 2005; 75(3):207–46. [PubMed: 15882775]
4. Maiese K. SIRT1 and stem cells: In the forefront with cardiovascular disease, neurodegeneration and cancer. World J Stem Cells. 2015; 7(2):235–42. [PubMed: 25815111]
5. Maiese K, Chong ZZ, Shang YC, Wang S. mTOR: on target for novel therapeutic strategies in the nervous system. Trends Mol Med. 2013; 19(1):51–60. [PubMed: 23265840]
6. Maiese K. Moving to the Rhythm with Clock (Circadian) Genes, Autophagy, mTOR, and SIRT1 in Degenerative Disease and Cancer. Curr Neurovasc Res. 2017; 14(3):299–304. [PubMed: 28721811]

7. Mravec B, Horvathova L, Padova A. Brain Under Stress and Alzheimer's Disease. Cell Mol Neurobiol. 2017
8. Fann DY, Ng GY, Poh L, Arumugam TV. Positive effects of intermittent fasting in ischemic stroke. Exp Gerontol. 2017; 89:93–102. [PubMed: 28115234]
9. Murphy KE, Park JJ. Can Co-Activation of Nrf2 and Neurotrophic Signaling Pathway Slow Alzheimer's Disease? International journal of molecular sciences. 2017; 18(6)
10. Peixoto CA, de Oliveira WH, da Rocha Araujo SM, Nunes AKS. AMPK activation: Role in the signaling pathways of neuroinflammation and neurodegeneration. Exp Neurol. 2017
11. Xu W, Liu J, Ma D, Yuan G, Lu Y, Yang Y. Capsaicin reduces Alzheimer-associated tau changes in the hippocampus of type 2 diabetes rats. PLoS One. 2017; 12(2):e0172477. [PubMed: 28225806]
12. Zhang ZH, Wu QY, Zheng R, Chen C, Chen Y, Liu Q, et al. Selenomethionine mitigates cognitive decline by targeting both tau hyperphosphorylation and autophagic clearance in an Alzheimer's disease mouse model. J Neurosci. 2017
13. Zheng H, Jia L, Liu CC, Li Zhong ZR, Yang L, Chen XF, et al. TREM2 promotes microglial survival by activating Wnt/beta-catenin pathway. J Neurosci. 2017
14. Chong ZZ, Shang YC, Wang S, Maiese K. Shedding new light on neurodegenerative diseases through the mammalian target of rapamycin. Prog Neurobiol. 2012; 99(2):128–48. [PubMed: 22980037]
15. Maiese K. FoxO Proteins in the Nervous System. Anal Cell Pathol (Amst). 2015; 2015:569392. [PubMed: 26171319]
16. Saha P, Biswas SC. Amyloid-beta induced astrocytosis and astrocyte death: Implication of FoxO3a-Bim-caspase3 death signaling. Mol Cell Neurosci. 2015; 68:203–11. [PubMed: 26260111]
17. Shi C, Zhu J, Leng S, Long D, Luo X. Mitochondrial FOXO3a is involved in amyloid beta peptide-induced mitochondrial dysfunction. Journal of bioenergetics and biomembranes. 2016; 48(3):189–96. [PubMed: 26782277]
18. Weigel D, Jurgens G, Kuttner F, Seifert E, Jackle H. The homeotic gene fork head encodes a nuclear protein and is expressed in the terminal regions of the Drosophila embryo. Cell. 1989; 57(4):645–58. [PubMed: 2566386]
19. Maiese K. Forkhead Transcription Factors: Vital Elements in Biology and Medicine. Advances in Experimental Medicine and Biology, Springer Science and Business Media. 2010:665.
20. Maiese K, Chong ZZ, Shang YC. "Sly as a FOXO": New paths with Forkhead signaling in the brain. Curr Neurovasc Res. 2007; 4(4):295–302. [PubMed: 18045156]
21. Maiese K, Chong ZZ, Shang YC, Hou J. Clever cancer strategies with FoxO transcription factors. Cell Cycle. 2008; 7(24):3829–39. [PubMed: 19066462]
22. Maiese K, Hou J, Chong ZZ, Shang YC. A fork in the path: Developing therapeutic inroads with FoxO proteins. Oxid Med Cell Longev. 2009; 2(3):119–29. [PubMed: 20592766]
23. Farhan M, Wang H, Gaur U, Little PJ, Xu J, Zheng W. FOXO Signaling Pathways as Therapeutic Targets in Cancer. Int J Biol Sci. 2017; 13(7):815–27. [PubMed: 28808415]
24. Maiese K, Chong ZZ, Shang YC, Hou J. FoxO proteins: cunning concepts and considerations for the cardiovascular system. Clin Sci (Lond). 2009; 116(3):191–203. [PubMed: 19118491]
25. Maiese K, Chong ZZ, Shang YC, Hou J. A "FOXO" in sight: targeting Foxo proteins from conception to cancer. Med Res Rev. 2009; 29(3):395–418. [PubMed: 18985696]
26. Biggs WH 3rd, Cavenee WK, Arden KC. Identification and characterization of members of the FKHR (FOX O) subclass of winged-helix transcription factors in the mouse. Mamm Genome. 2001; 12(6):416–25. [PubMed: 11353388]
27. Huang H, Tindall DJ. Dynamic FoxO transcription factors. J Cell Sci. 2007; 120(Pt 15):2479–87. [PubMed: 17646672]
28. Clark KL, Halay ED, Lai E, Burley SK. Co-crystal structure of the HNF-3/fork head DNA-recognition motif resembles histone H5. Nature. 1993; 364(6436):412–20. [PubMed: 8332212]
29. Tsai KL, Sun YJ, Huang CY, Yang JY, Hung MC, Hsiao CD. Crystal structure of the human FOXO3a-DBD/DNA complex suggests the effects of post-translational modification. Nucleic Acids Res. 2007; 35(20):6984–94. [PubMed: 17940099]

30. Chong ZZ, Hou J, Shang YC, Wang S, Maiese K. EPO Relies upon Novel Signaling of Wnt1 that Requires Akt1, FoxO3a, GSK-3beta, and beta-Catenin to Foster Vascular Integrity During Experimental Diabetes. Curr Neurovasc Res. 2011; 8(2):103–20. [PubMed: 21443457]

31. Lehtinen MK, Yuan Z, Boag PR, Yang Y, Villen J, Becker EB, et al. A conserved MST-FOXO signaling pathway mediates oxidative-stress responses and extends life span. Cell. 2006; 125(5): 987–1001. [PubMed: 16751106]

32. Scodelaro Bilbao P, Boland R. Extracellular ATP regulates FoxO family of transcription factors and cell cycle progression through PI3K/Akt in MCF-7 cells. Biochim Biophys Acta. 2013; 1830(10):4456–69. [PubMed: 23742826]

33. Van Der Heide LP, Hoekman MF, Smidt MP. The ins and outs of FoxO shuttling: mechanisms of FoxO translocation and transcriptional regulation. Biochem J. 2004; 380(Pt 2):297–309. [PubMed: 15005655]

34. Maiese K, Chong ZZ, Hou J, Shang YC. The “O” class: crafting clinical care with FoxO transcription factors. Adv Exp Med Biol. 2009; 665:242–60. [PubMed: 20429429]

35. Hoekman MF, Jacobs FM, Smidt MP, Burbach JP. Spatial and temporal expression of FoxO transcription factors in the developing and adult murine brain. Gene Expr Patterns. 2006; 6(2): 134–40. [PubMed: 16326148]

36. van der Heide LP, Jacobs FM, Burbach JP, Hoekman MF, Smidt MP. FoxO6 transcriptional activity is regulated by Thr26 and Ser184, independent of nucleo-cytoplasmic shuttling. Biochem J. 2005; 391(Pt 3):623–9. [PubMed: 15987244]

37. Salih DA, Rashid AJ, Colas D, de la Torre-Ubieta L, Zhu RP, Morgan AA, et al. FoxO6 regulates memory consolidation and synaptic function. Genes Dev. 2012; 26(24):2780–801. [PubMed: 23222102]

38. Calabuig-Navarro V, Yamauchi J, Lee S, Zhang T, Liu YZ, Sadlek K, et al. FoxO6 Depletion Attenuates Hepatic Gluconeogenesis and Protects Against Fat-Induced Glucose Disorder in Mice. J Biol Chem. 2015

39. Gilels F, Paquette ST, Zhang J, Rahman I, White PM. Mutation of Foxo3 causes adult onset auditory neuropathy and alters cochlear synapse architecture in mice. J Neurosci. 2013; 33(47): 18409–24. [PubMed: 24259566]

40. Hou J, Wang S, Shang YC, Chong ZZ, Maiese K. Erythropoietin Employs Cell Longevity Pathways of SIRT1 to Foster Endothelial Vascular Integrity During Oxidant Stress. Curr Neurovasc Res. 2011; 8(3):220–35. [PubMed: 21722091]

41. Maiese K, Li F, Chong ZZ. Erythropoietin in the brain: can the promise to protect be fulfilled? Trends Pharmacol Sci. 2004; 25(11):577–83. [PubMed: 15491780]

42. Peng S, Zhao S, Yan F, Cheng J, Huang L, Chen H, et al. HDAC2 selectively regulates FOXO3a-mediated gene transcription during oxidative stress-induced neuronal cell death. J Neurosci. 2015; 35(3):1250–9. [PubMed: 25609639]

43. Chamorro ME, Wenker SD, Vota DM, Vittori DC, Nesse AB. Signaling pathways of cell proliferation are involved in the differential effect of erythropoietin and its carbamylated derivative. Biochim Biophys Acta. 2013; 1833(8):1960–8. [PubMed: 23602701]

44. Wang S, Chong ZZ, Shang YC, Maiese K. WISP1 neuroprotection requires FoxO3a post-translational modulation with autoregulatory control of SIRT1. Curr Neurovasc Res. 2013; 10(1): 54–60. [PubMed: 23151077]

45. Zeldich E, Chen CD, Colvin TA, Bove-Fenderson EA, Liang J, Tucker Zhou TB, et al. The neuroprotective effect of Klotho is mediated via regulation of members of the redox system. J Biol Chem. 2014; 289(35):24700–15. [PubMed: 25037225]

46. Rong Z, Pan R, Xu Y, Zhang C, Cao Y, Liu D. Hesperidin pretreatment protects hypoxia-ischemic brain injury in neonatal rat. Neuroscience. 2013; 255:292–9. [PubMed: 24076349]

47. Lee SJ, Seo BR, Choi EJ, Koh JY. The role of reciprocal activation of cAbl and Mst1 in the Oxidative death of cultured astrocytes. Glia. 2014; 62(4):639–48. [PubMed: 24464935]

48. Merkely B, Gara E, Lendvai Z, Skopal J, Leja T, Zhou W, et al. Signalling via PI3K/FOXO1A Pathway Modulates Formation and Survival of Human Embryonic Stem Cell-Derived Endothelial Cells. Stem Cells Dev. 2014

49. Xiong X, Xie R, Zhang H, Gu L, Xie W, Cheng M, et al. PRAS40 plays a pivotal role in protecting against stroke by linking the Akt and mTOR pathways. Neurobiol Dis. 2014; 66:43–52. [PubMed: 24583056]
50. Zhao Y, Yu Y, Tian X, Yang X, Li X, Jiang F, et al. Association Study to Evaluate FoxO1 and FoxO3 Gene in CHD in Han Chinese. PLoS One. 2014; 9(1):e86252. [PubMed: 24489705]
51. Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozena A, et al. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Autophagy. 2016; 12(1):1–222. [PubMed: 26799652]
52. Maiese K, Chong ZZ, Shang YC, Wang S. Targeting disease through novel pathways of apoptosis and autophagy. Expert opinion on therapeutic targets. 2012; 16(12):1203–14. [PubMed: 22924465]
53. Maiese K. Forkhead transcription factors: new considerations for alzheimer's disease and dementia. J Transl Sci. 2016; 2(4):241–7. [PubMed: 27390624]
54. Weikel KA, Cacicedo JM, Ruderman NB, Ido Y. Knockdown of GSK3beta Increases Basal Autophagy and AMPK Signaling in Nutrient-laden Human Aortic Endothelial Cells. Bioscience reports. 2016
55. Vidal RL, Figueroa A, Court FA, Thielen P, Molina C, Wirth C, et al. Targeting the UPR transcription factor XBP1 protects against Huntington's disease through the regulation of FoxO1 and autophagy. Hum Mol Genet. 2012; 21(10):2245–62. [PubMed: 22337954]
56. Omata Y, Lim YM, Akao Y, Tsuda L. Age-induced reduction of autophagy-related gene expression is associated with onset of Alzheimer's disease. American journal of neurodegenerative disease. 2014; 3(3):134–42. [PubMed: 25628964]
57. Shang YC, Chong ZZ, Hou J, Maiese K. FoxO3a governs early microglial proliferation and employs mitochondrial depolarization with caspase 3, 8, and 9 cleavage during oxidant induced apoptosis. Curr Neurovasc Res. 2009; 6(4):223–38. [PubMed: 19807657]
58. Shang YC, Chong ZZ, Hou J, Maiese K. The forkhead transcription factor FoxO3a controls microglial inflammatory activation and eventual apoptotic injury through caspase 3. Curr Neurovasc Res. 2009; 6(1):20–31. [PubMed: 19355923]
59. Chong ZZ, Li F, Maiese K. Group I Metabotropic Receptor Neuroprotection Requires Akt and Its Substrates that Govern FOXO3a, Bim, and beta-Catenin During Oxidative Stress. Curr Neurovasc Res. 2006; 3(2):107–17. [PubMed: 16719794]
60. Chong ZZ, Lin SH, Maiese K. The NAD+ precursor nicotinamide governs neuronal survival during oxidative stress through protein kinase B coupled to FOXO3a and mitochondrial membrane potential. J Cereb Blood Flow Metab. 2004; 24(7):728–43. [PubMed: 15241181]
61. Maiese K, Li F, Chong ZZ. New avenues of exploration for erythropoietin. Jama. 2005; 293(1):90–5. [PubMed: 15632341]
62. Chong ZZ, Maiese K. Erythropoietin involves the phosphatidylinositol 3-kinase pathway, 14-3-3 protein and FOXO3a nuclear trafficking to preserve endothelial cell integrity. Br J Pharmacol. 2007; 150(7):839–50. [PubMed: 17339844]
63. Anitha M, Gondha C, Sutliff R, Parsadanian A, Mwangi S, Sitaraman SV, et al. GDNF rescues hyperglycemia-induced diabetic enteric neuropathy through activation of the PI3K/Akt pathway. J Clin Invest. 2006; 116(2):344–56. [PubMed: 16453021]
64. Zheng WH, Kar S, Quirion R. FKHRL1 and its homologs are new targets of nerve growth factor Trk receptor signaling. J Neurochem. 2002; 80(6):1049–61. [PubMed: 11953455]
65. Zhu W, Bijur GN, Styles NA, Li X. Regulation of FOXO3a by brain-derived neurotrophic factor in differentiated human SH-SY5Y neuroblastoma cells. Brain Res Mol Brain Res. 2004; 126(1):45–56. [PubMed: 15207915]
66. Kandula V, Kosuru R, Li H, Yan D, Zhu Q, Lian Q, et al. Forkhead box transcription factor 1: role in the pathogenesis of diabetic cardiomyopathy. Cardiovasc Diabetol. 2016; 15(1):44. [PubMed: 26956801]
67. Zeng Z, Wang X, Bhardwaj SK, Zhou X, Little PJ, Quirion R, et al. The Atypical Antipsychotic Agent, Clozapine, Protects Against Corticosterone-Induced Death of PC12 Cells by Regulating the Akt/FoxO3a Signaling Pathway. Mol Neurobiol. 2016

68. Iyer S, Han L, Bartell SM, Kim HN, Gubrij I, de Cabo R, et al. Sirtuin1 (Sirt1) promotes cortical bone formation by preventing beta-catenin sequestration by FoxO transcription factors in osteoblast progenitors. J Biol Chem. 2014; 289(35):24069–78. [PubMed: 25002589]
69. Chong ZZ, Shang YC, Wang S, Maiese K. SIRT1: New avenues of discovery for disorders of oxidative stress. Expert opinion on therapeutic targets. 2012; 16(2):167–78. [PubMed: 22233091]
70. Chong ZZ, Wang S, Shang YC, Maiese K. Targeting cardiovascular disease with novel SIRT1 pathways. Future Cardiol. 2012; 8(1):89–100. [PubMed: 22185448]
71. Maiese K, Chong ZZ, Shang YC, Wang S. Translating cell survival and cell longevity into treatment strategies with SIRT1. Rom J Morphol Embryol. 2011; 52(4):1173–85. [PubMed: 22203920]
72. Paraiso AF, Mendes KL, Santos SH. Brain activation of SIRT1: role in neuropathology. Mol Neurobiol. 2013; 48(3):681–9. [PubMed: 23615921]
73. Wang W, Yan C, Zhang J, Lin R, Lin Q, Yang L, et al. SIRT1 inhibits TNF-alpha-induced apoptosis of vascular adventitial fibroblasts partly through the deacetylation of FoxO1. Apoptosis. 2013; 18(6):689–701. [PubMed: 23479127]
74. Hariharan N, Maejima Y, Nakae J, Paik J, Depinho RA, Sadoshima J. Deacetylation of FoxO by Sirt1 Plays an Essential Role in Mediating Starvation-Induced Autophagy in Cardiac Myocytes. Circ Res. 2010; 107(12):1470–82. [PubMed: 20947830]
75. Guo P, Wang D, Wang X, Feng H, Tang Y, Sun R, et al. Effect and mechanism of fuzhisan and donepezil on the sirtuin 1 pathway and amyloid precursor protein metabolism in PC12 cells. Molecular medicine reports. 2016; 13(4):3539–46. [PubMed: 26936536]
76. Lin CL, Huang WN, Li HH, Huang CN, Hsieh S, Lai C, et al. Hydrogen-rich water attenuates amyloid beta-induced cytotoxicity through upregulation of Sirt1-FoxO3a by stimulation of AMP-activated protein kinase in SK-N-MC cells. Chem Biol Interact. 2015; 240:12–21. [PubMed: 26271894]
77. Maiese K, Li F, Chong ZZ, Shang YC. The Wnt signaling pathway: Aging gracefully as a protectionist? Pharmacol Ther. 2008; 118(1):58–81. [PubMed: 18313758]
78. Shang YC, Chong ZZ, Hou J, Maiese K. Wnt1, FoxO3a, and NF-kappaB oversee microglial integrity and activation during oxidant stress. Cell Signal. 2010; 22(9):1317–29. [PubMed: 20462515]
79. Maiese K. WISP1: Clinical Insights for a Proliferative and Restorative Member of the CCN Family. Curr Neurovasc Res. 2014; 11(4):378–89. [PubMed: 25219658]
80. Maiese K. Picking a bone with WISP1 (CCN4): new strategies against degenerative joint disease. J Transl Sci. 2016; 1(3):83–5. [PubMed: 26893943]
81. Maiese K, Chong ZZ, Shang YC. OutFOXOing disease and disability: the therapeutic potential of targeting FoxO proteins. Trends Mol Med. 2008; 14(5):219–27. [PubMed: 18403263]
82. Maiese K, Chong ZZ, Hou J, Shang YC. Oxidative stress: Biomarkers and novel therapeutic pathways. Exp Gerontol. 2010; 45(3):217–34. [PubMed: 20064603]
83. Wang R, Islam BN, Bridges A, Sharman SK, Hu M, Hou Y, et al. cGMP Signaling Increases Antioxidant Gene Expression by Activating Forkhead Box O3A in the Colon Epithelium. Am J Pathol. 2017; 187(2):377–89. [PubMed: 27998725]
84. Yu S, Yu Y, Zhang W, Yuan W, Zhao N, Li Q, et al. FOXO3a promotes gastric cancer cell migration and invasion through the induction of cathepsin L. Oncotarget. 2016
85. Afanas'ev I. Signaling of reactive oxygen and nitrogen species in Diabetes mellitus. Oxid Med Cell Longev. 2010; 3(6):361–73. [PubMed: 21311214]
86. Maiese K. FoxO Transcription Factors and Regenerative Pathways in Diabetes Mellitus. Curr Neurovasc Res. 2015; 12(4):404–13. [PubMed: 26256004]
87. Akasaki Y, Alvarez-Garcia O, Saito M, Carames B, Iwamoto Y, Lotz MK. FOXO transcription factors support oxidative stress resistance in human chondrocytes. Arthritis & rheumatology (Hoboken, NJ). 2014; 66(12):3349–58.
88. Zhao Y, Sun Y, Ding Y, Wang X, Zhou Y, Li W, et al. GL-V9, a new synthetic flavonoid derivative, ameliorates DSS-induced colitis against oxidative stress by up-regulating Trx-1 expression via activation of AMPK/FOXO3a pathway. Oncotarget. 2015; 6(28):26291–307. [PubMed: 26327408]

89. Kim YR, Lee EK, Kim DH, Kim KM, Lee B, An HJ, et al. PPARalpha activation by MHY908 attenuates age-related renal inflammation through modulation of the ROS/Akt/FoxO1 pathway. Exp Gerontol. 2017; 92:87–95. [PubMed: 28323024]

90. Guo J, Cheng J, North BJ, Wei W. Functional analyses of major cancer-related signaling pathways in Alzheimer's disease etiology. Biochim Biophys Acta. 2017; 1868(2):341–58. [PubMed: 28694093]

91. Shafi O. Inverse relationship between Alzheimer's disease and cancer, and other factors contributing to Alzheimer's disease: a systematic review. BMC neurology. 2016; 16(1):236. [PubMed: 27875990]

92. Fernandez AM, Hervas R, Dominguez-Fraile M, Garrido VN, Gomez-Gutierrez P, Vega M, et al. Blockade of the Interaction of Calcineurin with FOXO in Astrocytes Protects Against Amyloid-beta-Induced Neuronal Death. J Alzheimers Dis. 2016; 52(4):1471–8. [PubMed: 27079728]

93. Xu G, Liu J, Yoshimoto K, Chen G, Iwata T, Mizusawa N, et al. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induces expression of p27(kip(1)) and FoxO3a in female rat cerebral cortex and PC12 cells. Toxicol Lett. 2014; 226(3):294–302. [PubMed: 24594276]

94. Hong YK, Lee S, Park SH, Lee JH, Han SY, Kim ST, et al. Inhibition of JNK/dFOXO pathway and caspases rescues neurological impairments in Drosophila Alzheimer's disease model. Biochem Biophys Res Commun. 2012; 419(1):49–53. [PubMed: 22326868]

95. Saleem S, Biswas SC. Tribbles Pseudokinase 3 Induces Both Apoptosis and Autophagy in Amyloid-beta-induced Neuronal Death. J Biol Chem. 2017; 292(7):2571–85. [PubMed: 28011637]

96. Kajihara T, Jones M, Fusi L, Takano M, Feroze-Zaidi F, Pirianov G, et al. Differential expression of FOXO1 and FOXO3a confers resistance to oxidative cell death upon endometrial decidualization. Mol Endocrinol. 2006; 20(10):2444–55. [PubMed: 16709600]