

Review

The FOX Family: Key Regulators in Aging-Related Pathways

Zhigang Zhou^{1,2,†}, Jialin Li^{3,†}, Yuanyuan Yang^{3,4}, Shusheng Huang^{1,3},
Xiangrong Li^{3,4}, Xu Liu¹, Jian Tu^{3,4,*}

¹Guangxi Key Laboratory of Diabetic Systems Medicine, Guilin Medical University, 541199 Guilin, Guangxi, China

²Department of Anesthesiology, The Second Affiliated Hospital of Guilin Medical University, 541199 Guilin, Guangxi, China

³College of Pharmacy, Guilin Medical University, 541199 Guilin, Guangxi, China

⁴Guangxi Key Laboratory of Molecular Medicine in Liver Injury and Repair, the First Affiliated Hospital of Guilin Medical University, 541001 Guilin, Guangxi, China

*Correspondence: tujian@glmu.edu.cn (Jian Tu)

†These authors contributed equally.

Academic Editor: Amancio Carnero Moya

Submitted: 7 March 2026 Revised: 20 May 2026 Accepted: 27 May 2026 Published: 20 October 2026

Abstract

The Forkhead box (FOX) family comprises a group of transcription factors distinguished by a wing-like helix structure in their DNA-binding domain and encompasses 19 subfamilies, including Forkhead Box O (FOXO), Forkhead Box M (FOX M), and Forkhead Box P (FOX P), among others. In recent years, the integral involvement of aging regulation, characterized as a genetically regulated process of progressive functional decline, in aging regulation has been highlighted by accumulating evidence. Specifically, FOXO up-regulates inhibitors p21 and p27, leading to cell cycle arrest, resistance to enhances oxidative stress resistance by activating enzymes such as superoxide dismutase (SOD) and catalase (CAT), promotes genomic stability by activating DNA repair through Growth Arrest and DNA Damage-Inducible 45 (GADD45), and initiates autophagy by targeting Beclin 1 (BECN1) and Unc-51 like autophagy activating kinase 2 (ULK2) under stress conditions when the Phosphoinositide 3-kinase (PI3K) - Protein Kinase B (Akt) axis is inhibited. In contrast, FOX M, specifically for FOX M1, has been shown to promote the cell proliferation by antagonizing the p16-pRb axis and the p53 signaling pathway, enhancing DNA damage repair capacity by modulating factors such as Nijmegen breakage syndrome protein (NBS1), and mitigating oxidative stress by regulating antioxidant enzymes such as SOD. Furthermore, FOX P can induce senescence by activating the p53/p21 axis and generating Reactive Oxygen Species (ROS). These processes mentioned above can regulate cellular senescence. Importantly, dysregulation of FOX members has been implicated in the pathogenesis of major aging-related diseases, including neurodegenerative disorders, cardiovascular diseases, and metabolic disorders. These findings underscore the central role of the FOX family in aging-related pathways, highlight its potential as a therapeutic targets to mitigate aging-associated diseases.

Keywords: aging; Forkhead box family; cell senescence; Forkhead Box O; Forkhead Box M; Forkhead Box P

1. Introduction

Aging is a genetically regulated progressive process of systemic functional decline that involves multiple levels including organism, tissue, cell, and molecular [1,2], which impairs physiological functions and increases susceptibility to chronic diseases [3]. Recognized as a kind of stress response [4], cell senescence forms a fundamental basis for organismal aging and mortality and contributes to homeostasis maintenance. Several theories have been proposed to explain the molecular mechanisms, including free radical, telomere, and DNA damage hypotheses of aging [5,6]. Given the profound impact of aging on health and disease, molecular regulators can be elucidated to integrate these senescent mechanisms as a crucial focus.

Chronic inflammation accelerates the senescence of immune cells, resulting in weakened immune function and an inability to clear senescent cells and inflammatory factors, which creates a vicious cycle of inflammation and senescence [7,8]. Forkhead box (FOX) family encompasses 19 subfamilies such as Forkhead Box O (FOXO),

Forkhead Box M (FOX M), Forkhead Box P (FOX P), and so on. The family comprises a group of transcription factors characterized by a wing-like helix structure in the DNA-binding domain [9,10,11], extensively studied in the context of inflammatory immunity and cancer. In the immune system, FOXO, especially FOXO3, suppresses Nuclear Factor kappa-B (NF-κB) and Signal Transducer and Activator of Transcription 3 (STAT3) signaling in T cells and macrophages, thereby down-regulating Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), and Inducible Nitric Oxide Synthase (iNOS) to maintain immune homeostasis [12]. FOX M1 in FOX M promotes pro-inflammatory responses by driving the expression of cytokines such as IL-6 and TNF-α in immune cells, and contributes to immune evasion by shaping an immunosuppressive tumor microenvironment when up-regulated in cancers [13,14]. FOX P3, belonging to FOX P family, represses Interleukin-2 (IL-2) and Interferon-gamma (IFN-γ) while inducing Interleukin-10 (IL-10) and Transforming Growth Factor-beta (TGF-β), thereby establishing pe-



peripheral immune tolerance. Once FOXP3 is deficient, it will lead to fatal systemic inflammation [15]. Therefore, FOX members exhibit dual roles in cancer biology: FOXO exerts tumor-suppressive functions by inducing cell cycle arrest and promoting apoptosis [16]. Moreover, FOXP2 can maintain genome stability and control DNA repair genes as a tumor suppressor [9]. However, FOXM1 is frequently overexpressed in various malignancies, driving tumor progression by promoting cell proliferation, enhancing DNA repair capacity, and regulating antioxidant enzyme expression [17,18]. Interestingly, FOXA1 promotes or blocks epithelial-mesenchymal transition (EMT) in a tissue-specific manner depending on the cancer type [19]. Of note, both inflammatory immune dysregulation and carcinogenesis are intimately linked to the aging process: chronic inflammation serves as a key driver of aging, while aging-related immune dysfunction further exacerbates cancer risk. Within this framework, FOX family members, owing to their central roles in inflammation, immunity, and cancer, have increasingly been recognized as crucial regulators of aging. Emerging evidence demonstrates that FOXO, FOXM1, and FOXP subfamilies directly contribute to cell senescence and tissue homeostasis through modulating cell cycle, oxidative stress, DNA repair, and autophagy [20,21,22]. So, FOX family can be positioned as pivotal molecular hubs connecting inflammation, cancer, and aging.

Extensive research has established FOX members as pivotal regulators of fundamental biological processes, including embryonic development [23,24], tissue differentiation [25], metabolic homeostasis [26], and immune function [27]. In recent years, more and more advances in aging have progressively elucidated specific functions of FOX members between aging and cellular homeostasis. Specifically, FOXO subfamily delays cellular aging by inducing cell cycle arrest, counteracting oxidative stress, promoting DNA repair, and initiating autophagy by targeting autophagy-related genes including Beclin1 (*BECL1*), Autophagy related 14 (*ATG14*), and Unc-51 like autophagy activating kinase 2 (*ULK2*) [28,29]. FOXM1 influences aging by regulating cell cycle progression and proliferative capacity [30], while FOXP subfamily acts via mechanisms linked to cell cycle regulation [31]. Other members like FOXA can indirectly affect aging by regulating glucose and lipid metabolic balance [32].

FOX members coordinate interactions among inflammation, immunity, and aging. FOXO3 and FOXP3 exert anti-inflammatory and immune-tolerogenic effects, while FOXM1 promotes pro-inflammatory cytokine expression. In parallel, FOXO and FOXM1 can delay senescence via cell cycle arrest, DNA repair, and autophagy, whereas FOXP and FOXA1 may induce senescence. But FOXP is through the p53/p21 axis, while FOXA1 via p16^{INK4a} activation (Fig. 1).

Notably, dysregulation in the expression or activity of FOX members is directly linked to the pathogenesis of several major aging-related diseases including neurodegenerative, metabolic disorders, and cardiovascular diseases. Collectively, clarifying the precise mechanisms by which FOX members govern aging processes can reveal critical molecular targets for developing therapeutic strategies against aging and its associated pathologies. Therefore, this review aims to systematically outline the core functions and mechanisms of major FOX subfamilies such as FOXO, FOXM1, FOXP, and so on, in aging regulation, and to discuss the roles in related pathological processes, thereby providing a clear perspective for future research directions and translational applications in this field.

2. FOX in Aging Regulation

FOX family plays a central role in the aging process by regulating multiple key pathways. Specifically, different subfamilies contribute to the maintenance of cellular homeostasis and the attenuation of aging phenotypes through mechanisms such as inducing cell cycle arrest, enhancing antioxidant defenses, promoting DNA repair, and regulating autophagy (Table 1, Ref. [29,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58]). Among these members, FOXO subfamily, which acts as a direct regulator in the aforementioned pathways, has been the most extensively studied, and its anti-aging function has been most robustly demonstrated.

Among FOX members, FOXO primarily acts as a protective modulator that delays senescence through cell cycle arrest and stress resistance, while FOXM1 functions as a context-dependent modulator that promotes the proliferation and suppresses senescence but can also drive tumorigenesis when dysregulated. Differently, FOXP mainly serves as a downstream responder that induces senescence via the p53/p21 axis. Collectively, FOXO, FOXM1, and FOXP do not operate merely as autonomous drivers or passive responders. Rather, they function as integrated core modulators of the aging process at both genetic and pharmacological levels. At the genetic level, cyclic up-regulation of FOXM1 expression in mouse models ameliorates aging-related phenotypes and extends healthspan [20], whereas natural product-mediated activation of FOXO3 prolongs total lifespan in model organisms [59]. Pharmacological evidence further confirms this causal relationship. FOXO activators such as metformin and natural bioactive substances promote healthy longevity [60]. The FOXO4-p53 interfering peptide FOXO4-D-retro-inverso (DRI) alleviates senescent cell accumulation and enhances cognitive performance in aged animal models [61]. In addition, FOXM1 inhibitors exert potent senolytic effects to clear senescent cells [62,63].

In conclusion, FOX members serve as central regulators that sense diverse aging-related stress stimuli, in-

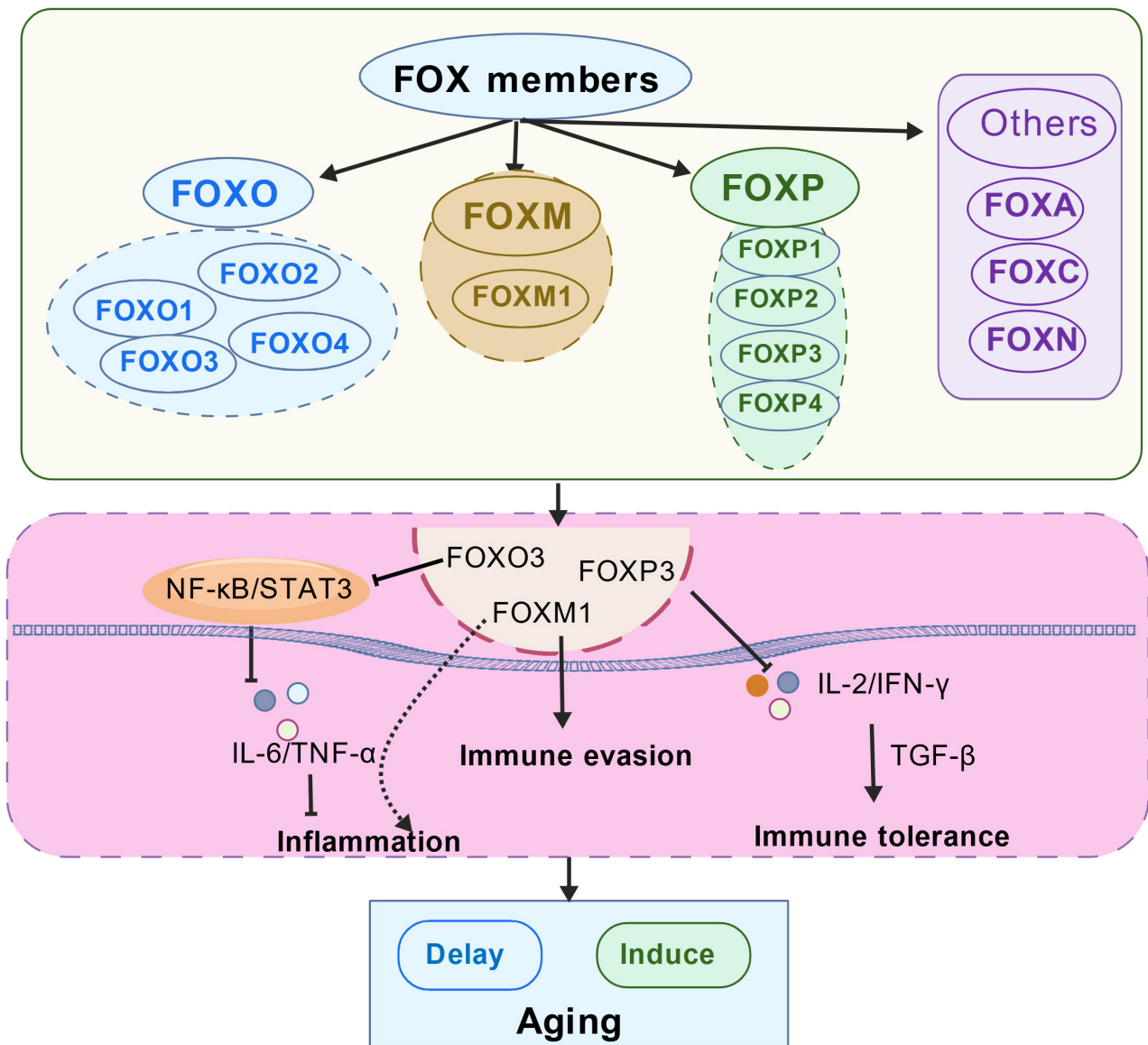


Fig. 1. Forkhead box (FOX) family in inflammation, immunity, and aging (by BioGDP). This schematic illustrates the pivotal role of FOX family including Forkhead Box O (FOXO), Forkhead Box M (FOXM), and Forkhead Box P (FOXP), in integrating immune regulation and aging processes. These subfamilies coordinate bidirectional signaling with inflammation, immunity, and aging. (1) FOX members are grouped into four subfamilies: FOXO, FOXM, FOXP, and others. FOXO subfamily includes FOXO1, FOXO2, FOXO3, and FOXO4. FOXM subfamily consists of FOXM1. FOXP subfamily includes FOXP1, FOXP2, FOXP3, and FOXP4. (2) FOXO3 suppresses pro-inflammatory signaling by inhibiting Nuclear Factor kappa-B (NF-κB) and Signal Transducer and Activator of Transcription 3 (STAT3), leading to down-regulation of Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α) associated with reduced inflammation and immune evasion. FOXP3 promotes immune tolerance by repressing Interleukin-2 (IL-2) and Interferon-gamma (IFN-γ) while inducing Transforming Growth Factor-beta (TGF-β). Conversely, FOXM1 drives pro-inflammatory responses by enhancing the expression of IL-6 and TNF-α. (3) Chronic inflammation drives inflammaging, while immunosenescence exacerbates immune dysfunction, forming a feedback loop that accelerates aging, as shown by the arrow from aging to immunity. This feedback loop accelerates the aging process. Thus, FOX family members serve as critical molecular hubs integrating these interconnected pathways.

cluding oxidative stress, DNA damage, and inflammation, and act as effector molecules that convert these signals into adaptive or pathological physiological consequences [33,34].

FOXO delays senescence, FOXM1 suppresses senescence, and FOXP induces senescence; the balance among these subfamilies determines the net aging outcome.

Table 1. FOX members in aging regulation.

FOX members	Aging outcome	Common mechanisms			Distinct mechanisms		Cell type-specific	References
		Cell cycle	DNA repair	Oxidative stress	Autophagy	Additional		
Forkhead Box O (FOXO)	Delays senescence	Promotes cell cycle arrest through p21/p27	Enhances DNA repair via Growth Arrest and DNA Damage-Inducible 45 (<i>GADD45</i>)	Enhances antioxidant defense	Activates <i>Beclin 1</i> (<i>BECN1</i>), Related Unc-51 Like Activating Kinase 2, (ULK2)		Protective in neurons, cardiomyocytes, hepatocytes/adipocytes	[29,33,35,36,48,49,51]
Forkhead Box M (FOXO, mainly FOXM1)	Suppresses senescence	Promotes cell cycle progression (Phase G1 to Phase S)	Enhances DNA Breakage Syndrome 1 (<i>NBS1</i>)	Indirectly reduces active Oxygen Species (ROS)		Inhibits p16-pRb/p19Arf-p53 pathways	Harmful in dopaminergic neurons, promotes vascular remodeling; affects immune cells	[34,37,38,39,50,52,53]
Forkhead Box P (FOXP, mainly FOXP3)	Induces senescence	Induces cell cycle arrest through p53/p21	Indirectly via p53	Promotes ROS generation		Activates p53/p21 axis to induce senescence	FOXP3 Tregs regulate late neuroinflammation, atherosclerosis, metabolic inflammation	[40,41,42,43,54,55,56]
Forkhead Box A (FOXA)	Pro-senescence	-	-	-	-	Target of Rapamycin (TOR) inhibition extends lifespan	-	[44,45]
Forkhead Box C (FOXC)	Drives cardiomyocyte senescence	-	-	-	-	Induced by telomere shortening	-	[46]
Forkhead Box N (FOXN)	Thymic rejuvenation	-	-	-	-	Maintains thymic function, reverses involution	-	[47]

Note: FOXM1 has been reported to regulate autophagy in certain cancer models through the HMMR/ATG7 or LC3 pathways, but direct evidence in aging is currently lacking [57,58].

2.1 FOXO in Aging Regulation

FOXO subfamily exerts the effects by regulating genes associated with diverse cellular functions, including apoptosis, the cell cycle, DNA repair, and oxidative stress. By inhibiting the cell cycle and exerting antioxidant effects, FOXO influences cell senescence processes, thereby conferring anti-aging effects. Among these, FOXO1, FOXO3, and other members are regarded as key regulatory factors in cell senescence and lifespan regulation.

Under normal physiological conditions, insulin and other growth factors activate the Phosphoinositide 3 (PI3K)-Protein Kinase B (Akt) signaling pathway, which leads to the phosphorylation of FOXO proteins. Subsequently, these phosphorylated proteins are translocated from the nucleus to the cytoplasm and degraded via the ubiquitin-proteasome pathway [64]. Conversely, under growth factor deprivation or stress stimuli, FOXO proteins relocate to the nucleus. There, they activate a series of target genes that promote cell cycle arrest, enhance stress resistance, or induce apoptosis. This regulatory mechanism is closely associated with organismal stress resistance and lifespan extension. For example, in the nematode *Caenorhabditis elegans* (*C. elegans*), Abnormal DAuer Formation protein 16 (*DAF-16*), as a kind of FOXO family homologue, has significantly prolonged lifespan by regulating genes associated with longevity and stress resistance [59]. In mammals, FOXO members such as FOXO4 (*AFX*), Forkhead Homolog in Rhabdomyosarcoma-Like 1 (*FKHRL1*), and Forkhead Homolog in Rhabdomyosarcoma (*FKHR*) function as homologues of *DAF-16* and modulate cellular responses to oxidative stress. Based on this, research in the mouse myoblast cell line C2C12 shows that constitutive expression of an active AFX variant (AFX-TM) blocks cell cycle progression at Stage G1 and G2. This effect is achieved by regulating the expression of stress-induced genes like Growth Arrest and DNA Damage-Inducible 45 (*GADD45*) and conferring oxidative stress resistance to the cells [35]. *GADD45* is a direct transcriptional target of FOXO, as its promoter contains FOXO binding sites. *GADD45* protein plays a pivotal role in multiple cellular functions, including DNA repair, cell cycle control, and responses to genotoxic stress [65]. Oxidative stress activates the *GADD45* promoter in a FOXO-dependent manner, leading to elevated mRNA and protein levels. This up-regulation, in turn, triggers G2 arrest, a phenomenon particularly pronounced in cells with inactivated p53. Through these actions, *GADD45* contributes to activating cell cycle checkpoints and promoting DNA repair, thereby maintaining genomic integrity [36]. Notably, in *C. elegans*, *DAF-16* responds to oxidative stress by translocating to the nucleus and activating stress-inducible genes, including *GADD45*. A similar mechanism operates in mammalian cells, where oxidative stress induces *GADD45* expression via FOXO members, leading to G2 arrest and enhancing cellular adaptation to stress.

Furthermore, research in multiple human longevity cohorts indicates that FOXO3 is associated with delayed aging, a role further supported by its ability to delay telomere attrition, promote cell self-renewal, and maintain genomic stability [33]. Studies in human cell lines and model organisms have shown that FOXO3 enhances cellular resistance to environmental stress partly through regulating autophagy and antioxidant responses. FOXO proteins promote the initiation of autophagy by activating key autophagy-related genes, including *BECN1*, *ATG14*, *ULK2*, etc. This process aids in clearing damaged organelles and protein aggregates, thereby maintaining intracellular homeostasis and delaying functional decline. For instance, the up-regulated expression of FOXO1 and FOXO3 in aging brain tissues has been shown to protect neurons from oxidative damage by inducing autophagy. All above can be seen in Fig. 2.

2.2 FOXM in Aging Regulation

In contrast to FOXO, which primarily delays aging through stress resistance and autophagy, FOXM subfamily exerts its effects mainly by sustaining proliferative capacity. FOXM1, a principal member of FOXM subfamily, comprises three main subtypes: FOXM1a, FOXM1b, and FOXM1c. FOXM1 expression is strongly correlated with cellular proliferation and is predominantly detected in actively dividing cells. In adult mammals, FOXM1 is largely confined to progenitor cells and regenerating tissues, but is frequently overexpressed in a wide range of human malignancies. Studies further suggest that amplification of FOXM1 gene may underpin the unique longevity mechanisms observed in species such as naked mole-rats and long-eared bats [66].

Beyond direct roles in driving proliferation, FOXM1 also indirectly influences processes like cell senescence and apoptosis. Regarding aging, FOXM1 is proposed to exert regulatory effects primarily by inhibiting key pathways that promote cell senescence [34,67]. The Anaphase-Promoting Complex/Cyclosome-Cdh1 (APC/C-Cdh1)-mediated degradation of FOXM1 is critical for proper cell cycle progression, and age-related dysregulation of this axis contributes to proliferative decline and senescence accumulation [68,69].

FOXM1 acts as a proliferation-specific transcription factor, driving the expression of multiple cell cycle progression-related genes and supporting tumor cell proliferation by promoting antioxidant gene expression, which mitigates oxidative stress. FOXM1 is broadly expressed in actively dividing cells and plays a pivotal role in regulating genes governing phase G2 of the cell cycle [37]. Through these functions, FOXM1 protects cells from premature aging induced by stress. FOXM1 transcriptional activity depends on upstream activation by cyclins, cyclin-dependent kinases, and Plk1.

FOXM1-mediated regulation of cell senescence involves complex mechanisms. Cell senescence represents a

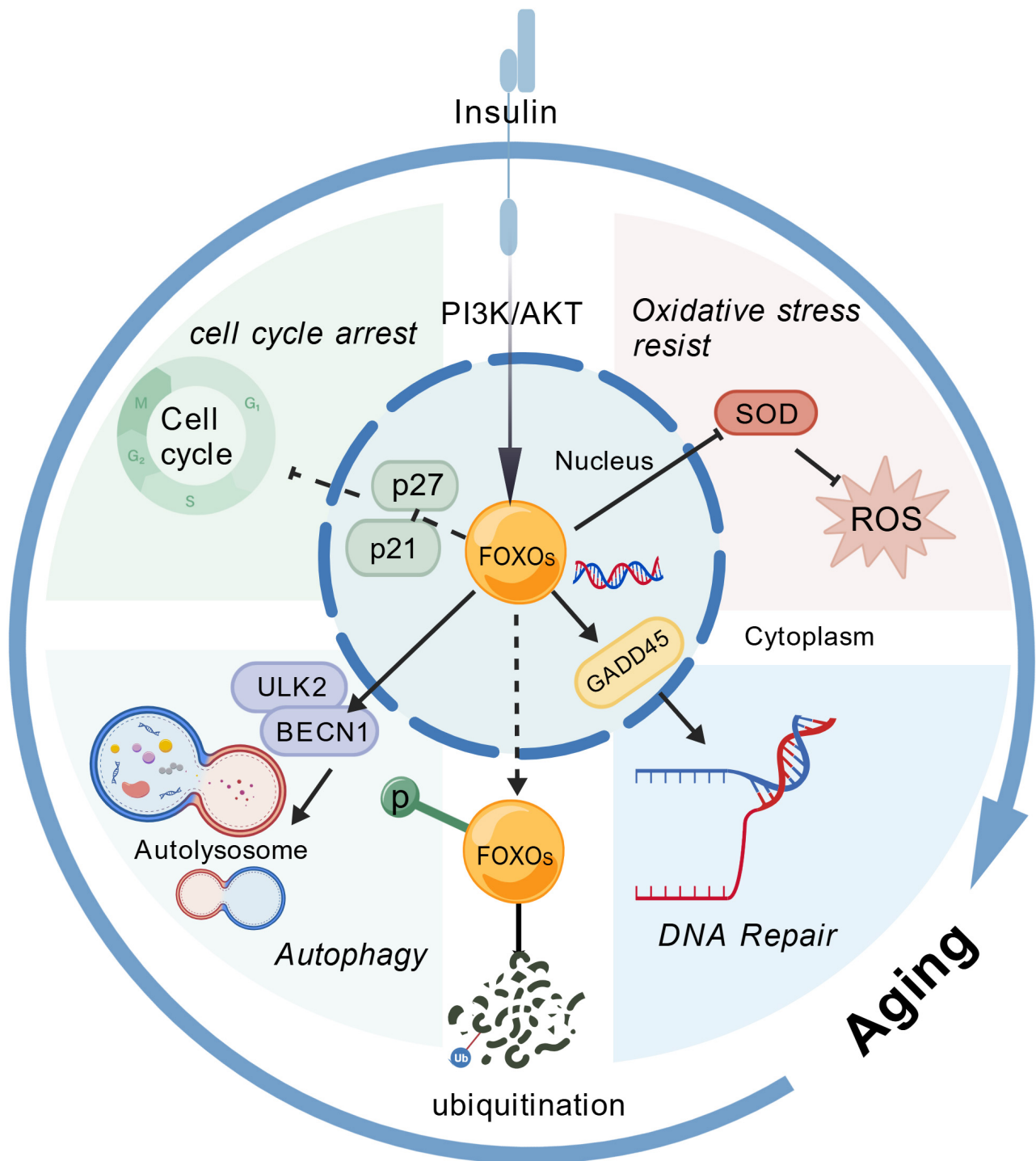


Fig. 2. Molecular mechanisms of FOXO in aging regulation (by BioGDP). FOXO is the central regulator of cell senescence and longevity. This schematic illustrates key pathways through which FOXO exerts its anti-aging effects as follows: (1) Inducing cell cycle arrest by up-regulating cyclin-dependent kinase inhibitors, e.g., p21, p27. (2) Enhancing antioxidant defenses through the activation of enzymes like superoxide dismutase (SOD) and catalase (CAT). (3) Promoting genomic stability by activating DNA repair genes. (4) Regulating autophagy initiation via genes such as *BECN1* and *ULK2* to clear the damaged cellular components. Together, these coordinated actions enhance stress resistance, maintain cellular homeostasis, and delay the aging process.

process governed by multiple signaling pathways. Among these, the p53-p21-pRb and p16-pRb pathways have been studied most extensively. Both p21 and p16 can inhibit Rb

phosphorylation and E2F activity, leading to cell cycle arrest. Senescent cells exhibit increased β -galactosidase activity, cell cycle arrest, and elevated expression of cyclin-

dependent kinase inhibitors such as p53, p21, and p16. Research indicates that elevated FOXM1 could antagonize the p16-pRb pathway, thereby protecting human cells from premature senescence induced by various stimuli [38]. In these senescence responses, the pRb protein may be crucial like p53. The pro-tumorigenic role of FOXM1 also involves activation of Bmi-1 and suppression of senescence mediated by the p19Arf-p53 pathway. Up-regulating FOXM1 expression antagonizes senescence-inducing factors by inhibiting the p19Arf-p53 pathway via Bmi-1 activation. Furthermore, p19Arf negatively regulates FOXM1 activity via protein-protein interaction as a tumor suppressor. FOXM1-mediated inhibition of the p19ARF-p53 pathway reduces cellular p19Arf levels, creating a feedback loop that amplifies the proliferative effects of FOXM1. Within this network, p53 serves as a primary regulator of cellular senescence, activating distinct gene expression profiles to inhibit the proliferation. The p53 protein can induce transient cell cycle arrest at Stage G1 or G2, trigger permanent senescence, or promote apoptosis under severe conditions. Conversely, ARF localizes to the nucleus by binding to Mouse Double Minute 2 (MDM2), antagonizing MDM2-mediated ubiquitination and degradation of p53, thereby stabilizing p53.

Up-regulation of FOXM1 also stimulates the expression of c-Myc and Bmi-1. FOXM1 regulates Bmi-1 expression via c-Myc. Both c-Myc and Bmi-1 are crucial for maintaining stem cell function. *In vitro* and *in vivo* studies demonstrate that Bmi-1 plays a key role in stem cell self-renewal and differentiation through multiple pathways [70], which can be up-regulated by Spalt Like Transcription Factor 4 (SALL4). The Hedgehog signaling pathway also contributes to stem cell regulation by suppressing genes at the INK4a locus, specifically for p16INK4a and p19ARF, and by influencing other factors such as telomerase, the transcription factor GATA Binding Protein 3 (GATA3), and the NF- κ B pathway. Ectopic expression of Bmi-1 protects keratinocytes from stress-induced apoptosis and counteracts pro-apoptotic effects in other cell models. Collectively, these genes and signaling pathways participate in determining stem cell fate, influencing processes including the prevention of senescence and apoptosis, the control of differentiation, and the promotion of proliferation. Therefore, FOXM1 up-regulation enhances intracellular Bmi-1 expression, which contributes to the inhibition of cellular senescence.

FOXM1 also mitigates oxidative stress damage in cancer cells by regulating intracellular reactive oxygen species levels. Mitochondrial Reactive Oxygen Species (ROS) levels are elevated in FOXM1-deficient cells, and ROS scavengers can reverse this effect. FOXM1 induces the expression of antioxidant enzymes such as manganese superoxide dismutase, catalase, and peroxisome peroxidase, which can assist in scavenging reactive oxygen species and protecting cells from oxidative damage. Furthermore, FOXM1 targets

key DNA repair factors like Nijmegen breakage syndrome protein (*NBS1*), modulating the expression to enhance DNA damage repair capacity and reduce cellular sensitivity to DNA damage [39]. Supporting a direct role in aging, research in premature aging mouse models shows that overexpression of truncated forms of FOXM1 can reverse aging phenotypes, reduce DNA damage, and restore aging-associated epigenetic marks [62], which is summarized in Fig. 3. A recent study integrating multiple techniques such as Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq) chromatin accessibility analysis, 4C-seq chromatin conformation capture, and Clustered Regularly Interspaced Short Palindromic Repeats - CRISPR associated protein 9 (CRISPR-Cas9) gene editing, has further revealed that FOXM1 could maintain a youthful chromatin accessibility profile by suppressing the Activator protein-1 (AP-1) complex. The study has found that decreasing FOXM1 expression leads to inactivation of the enhancer C10, reducing the downstream genes, thereby driving aging. Conversely, FOXM1 overexpression can partially reverse these aging-related chromatin changes [34].

Despite FOXM1 having anti-aging effects in certain contexts, it is frequently overexpressed in human malignancies and promotes tumorigenesis by driving proliferation, DNA repair, and immune evasion. This duality raises a critical question: how can FOXM1 be therapeutically harnessed to delay aging without increasing cancer risk? The answer may lie in intermittent or tissue-specific modulation, as suggested by studies showing that cyclic induction of FOXM1 *in vivo* delays aging phenotypes without causing tumors in short-term mouse models. However, long-term safety remains to be established [13].

2.3 FOXP in Aging Regulation

FOXP subfamily comprises four principal members: FOXP1, FOXP2, FOXP3, and FOXP4. Each member exerts distinct biological functions: firstly, FOXP1 primarily regulates B-cell development; secondly, FOXP2 regulates language development; thirdly, FOXP4 plays a pivotal role in T-cell development; and finally, FOXP3 is critical in tumor immunotherapy, as FOXP3 drives regulatory T cell (CD4⁺/CD25⁺ Treg) differentiation and function and induces cell cycle arrest [40,41].

FOXP exhibits a close association with the p53 signaling pathway, and both systems synergistically regulate processes of cellular senescence. The tumor suppressor p53 effectively inhibits tumor initiation and progression through multiple mechanisms, including the regulation of apoptosis, metabolic networks, and senescence [71]. Studies using human cancer cell lines *in vitro* have confirmed that genotoxic agent-induced p53 up-regulation enhances FOXP3 expression. Conversely, Nutlin-3, the MDM2 inhibitor, regulates FOXP3 in a p53-dependent manner. Mechanistically, FOXP3 induces senescence in the cell lines such as MCF7 and HCT116 by activating the p53/p21 pathway and pro-

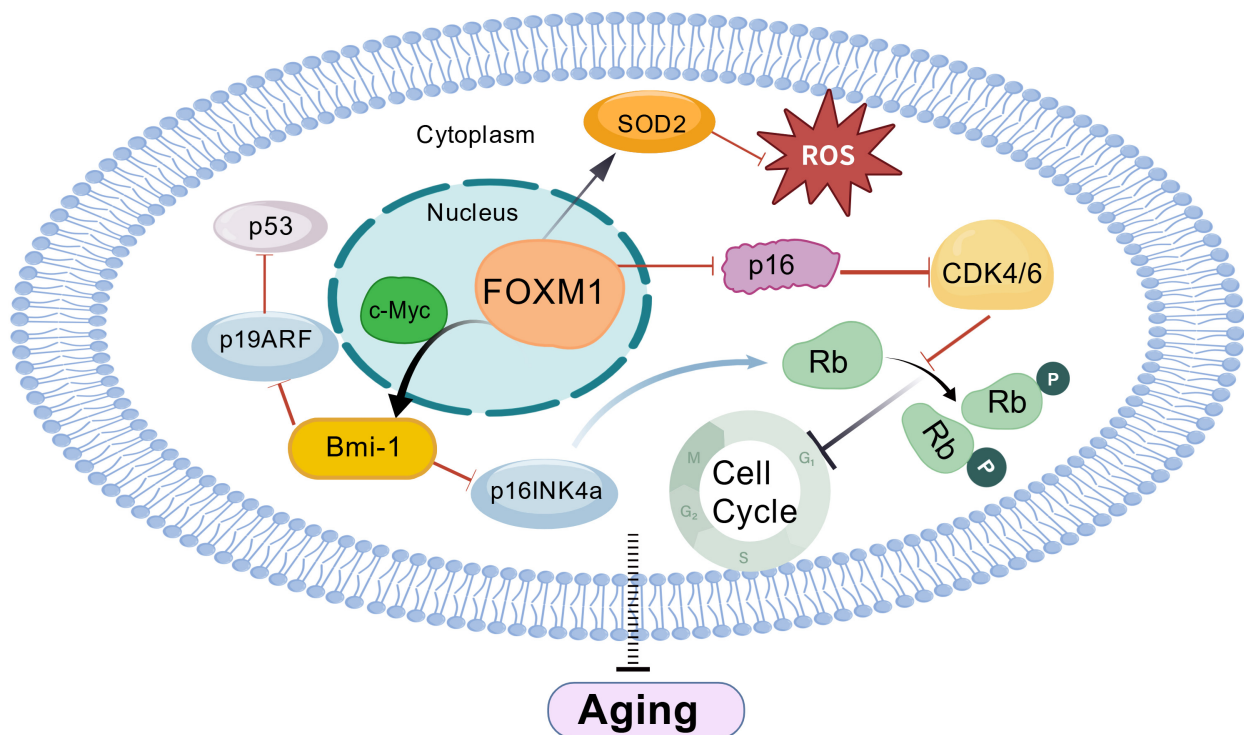


Fig. 3. FOXM1 regulation in antagonizing cellular senescence (by BioGDP). FOXM1 is a proliferation-associated transcription factor that counteracts aging by maintaining cellular replicative potential. This diagram depicts its multi-faceted roles: (1) Promoting cell cycle progression from G1 to S phase. (2) Indirectly mitigating oxidative stress by regulating cell proliferation. (3) Enhancing DNA damage repair capacity by modulating factors like Nijmegen breakage syndrome protein (*NBS1*). (4) Antagonizing p16-pRb senescence pathway, often through the up-regulation of stemness-associated genes such as Bmi-1. By sustaining proliferation and repressing key senescence inducers, FOXM1 protects against premature cell aging.

moting ROS generation. This connection is further supported by FOXM1 regulation, down-regulating p53 through miR-34a in human cancer cells [42,43]. These findings collectively confirm the close interaction between FOXM1 members and the p53 signaling pathway, and reveal a key regulatory mechanism underlying cell senescence (Fig. 4).

Beyond the canonical role of FOXM1 in the p53 pathway, FOXM1 has emerged as a critical regulator of stem cell senescence [72]. In a mouse model of skeletal aging, FOXM1 deficiency in bone marrow mesenchymal stem cells (MSCs) leads to accelerated cell senescence and impaired osteogenic differentiation, while FOXM1 overexpression rescues these age-related defects. These findings position FOXM1 as a gatekeeper of cell senescence in the skeletal system.

FOXM1 also appears to influence immune aging. Single-cell transcriptomics of peripheral T cells from healthy individuals across age groups has identified FOXM1 as a key component of young-specific regulons, which are associated with T-cell self-renewal capacity, whereas old-specific regulons are linked to effector/terminal differentiation and exhaustion. This finding extends the role of FOXM1 from skeletal stem cell aging to immunosenescence [73].

2.4 Other FOX Members in Aging Regulation

In addition to the three major subfamilies discussed above, other FOX members also indirectly influence aging through crosstalk between metabolic and epigenetic regulation. For example, FOXA1 exerts its pro-senescence function through direct transcriptional activation of p16INK4a as validated through the cell experiments *in vitro* [44,74]. The Target of Rapamycin (TOR) pathway regulates lifespan in *C. elegans* by inhibiting FOXA (PHA-4: under sufficient nutrients), activating S6K to suppress defective pharyngeal development protein 4 (PHA-4) and shorten lifespan, under nutrient restriction or TOR inhibition, and increasing PHA-4 activity to extend lifespan (animal study, nematodes) [45]. In patients with heart failure, cardiomyocytes show shortened telomeres, which will induce chromatin decompaction and FOXM1 up-regulation, promote cardiomyocyte senescence, mitochondrial dysfunction, and contractile impairment. FOXM1 knockdown rescues these phenotypes, supported through human cell experiments *in vitro* and clinical specimen analysis [46]. FOXM1 maintains thymic epithelial function, leading to thymic involution with its age-related decline, and restoring the expression by reversing thymic aging as confirmed through animal experiments and human tissue analysis [47].

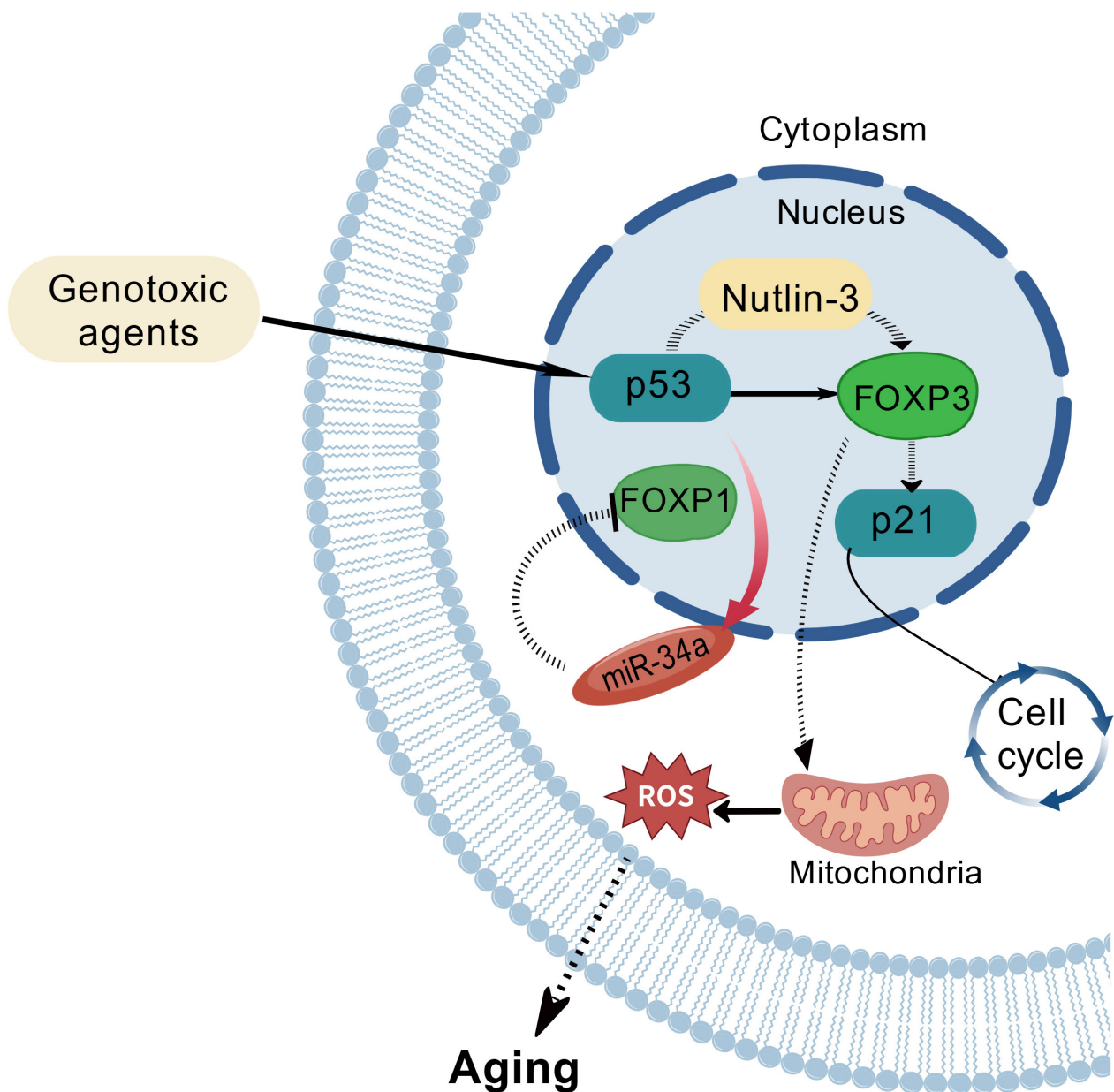


Fig. 4. FOXF involvement in aging regulation via the p53 pathway (by BioGDP). Members of FOXF subfamily, particularly FOXF1 and FOXF3, participate in modulating cell senescence through intricate crosstalk with the p53 signaling network. This schematic highlights the cooperative mechanisms: (1) FOXF3 expression is upregulated by p53 in response to genotoxic stress. (2) FOXF3 can induce senescence by activating the p53/p21 axis and promoting Reactive Oxygen Species (ROS) generation in turn. (3) FOXF1 is down-regulated by the p53/miR-34a axis, forming a negative feedback loop. These interactions position FOXF family as critical modulators at the intersection of tumor suppression and aging regulation.

3. FOX Family in Aging-Related Diseases

Aging is not an isolated process. As the primary risk factor for many chronic diseases, it is closely linked to an individual's health span. The role of FOX family in cellular aging extends to tissue and organism levels. Consequently, these factors influence the onset and progression of aging-related diseases. The specific roles of FOX family in several major aging-related conditions can be focused on, including neurodegenerative diseases, metabolic disorders,

and cardiovascular diseases, which are aimed at connecting the fundamental aging mechanism with clinical diseases. This approach provides a broader view of systemic functions about FOX family and potential therapeutic targets.

3.1 Neurodegenerative Diseases

Neurodegenerative diseases are common central nervous system disorders associated with aging. Their incidence strongly correlates with advancing age [75]. Among

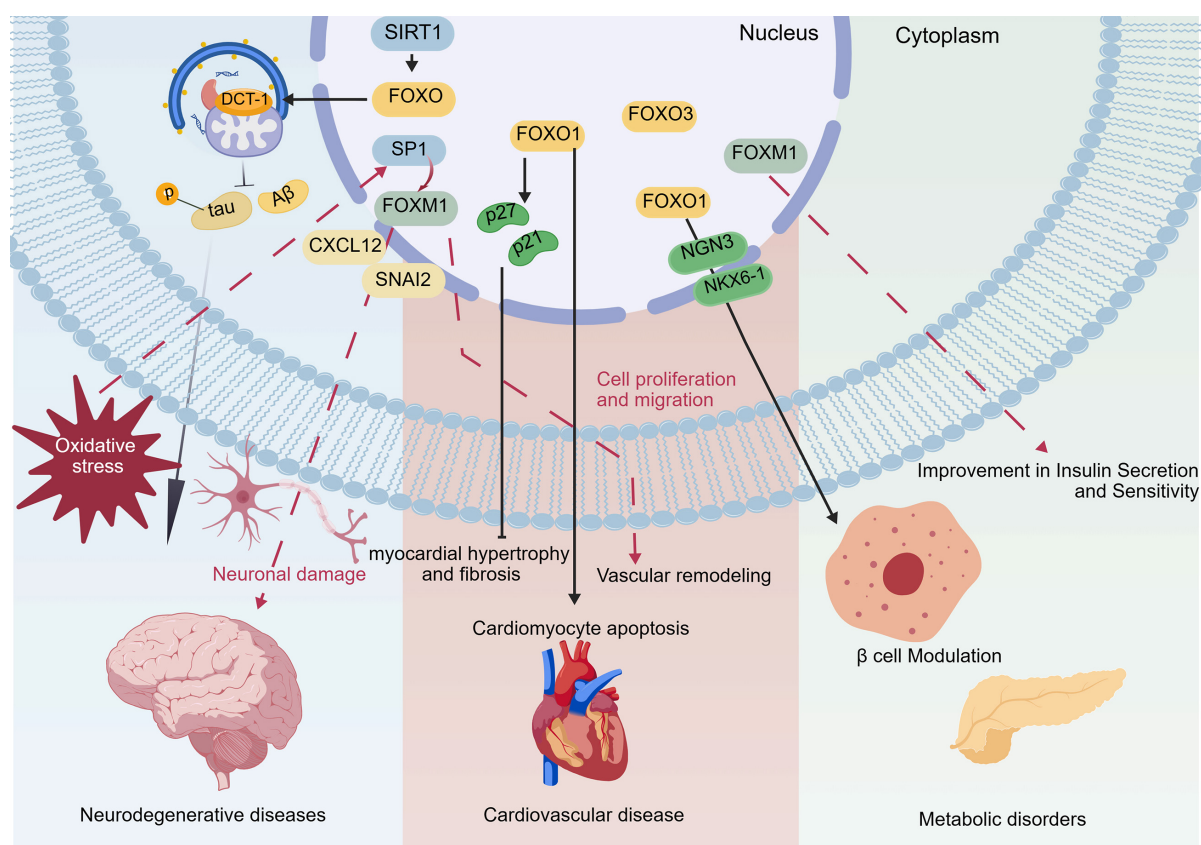


Fig. 5. FOX family in aging-related diseases (by BioGDP). This diagram illustrates the central role of FOX family in three major aging-related diseases: neurodegenerative, cardiovascular, and metabolic disorders. Acting as key signaling hubs, FOX proteins integrate aging-related stress signals and regulate downstream genes and cellular processes that drive disease progression. (1) In neurodegenerative diseases, the SIRT1–FOXO axis enhances mitophagy via targets DAF-16/FOXO-Controlled Tumor suppressor related 1 (*DCT-1*), aiding clearance of Aβ and pathological tau. FOXM1 shows context-dependent roles: its suppression may disrupt homeostasis, whereas acute stress-induced expression can worsen neuronal damage. Specificity Protein 1 (*SP1*)-mediated FOXM1 up-regulation promotes Snail Family Transcriptional Repressor 2 (*SNAI2*) and C-X-C Motif Chemokine Ligand 12 (*CXCL12*), accelerating dopaminergic neuron loss. (2) In cardiovascular disease, FOXO1 exerts dual effects: it protects the heart by activating p21/p27 and antioxidant pathways to suppress hypertrophy and fibrosis, yet excessive FOXO1 can trigger cardiomyocyte apoptosis. FOXO3 reduces ischemia-reperfusion injury via antioxidant and autophagic genes, while FOXM1 drives vascular remodeling through cell proliferation and migration. (3) In metabolic disease, FOXO1 regulates pancreatic β-cell function and survival through genes including Neurogenin-3 (*NGN3*) and NK6 Homeobox 1 (*NKX6-1*), and correlates inversely with insulin sensitivity. Modulating FOXM1 improves insulin secretion and sensitivity.

these, Alzheimer’s disease (AD) and Parkinson’s disease (PD) are the most prevalent, with progressive neuronal loss and functional decline [76].

AD, a common aging-related neurodegenerative disorder, is characterized by aging-exacerbated mitochondrial dysfunction that drives early cognitive decline in animal models [48], which occurs through disrupted neuronal energy metabolism, increased production of ROS, subsequent oxidative damage, and neuroinflammation [77,78]. Further research reveals that FOXO acts as a conserved downstream effector of Sirtuin 1 (*SIRT1*). FOXO can upregulate targets like DAF-16/FOXO-Controlled Tumor suppressor related 1 (*DCT-1*) to activate mitophagy. This clearance pathway reduces Aβ deposits and hyperphosphorylated tau protein, ultimately improving cognitive performance. These findings

highlight the SIRT1-FOXO autophagy axis as a key pathway to maintain cellular homeostasis against aging and degeneration [79,80]. FOXM1 is reported to play a dual role in AD. In the hippocampus of individuals with Down syndrome, a high AD risk, FOXM1 expression remains suppressed due to persistent miR-802 overexpression, which likely impairs the normal homeostatic function [81]. In contrast, under acute oxidative stress relevant to AD, FOXM1 is rapidly induced as part of the stress response. This induction potentially promotes aberrant cell-cycle activity and contributes to neuronal damage [82].

PD is a common degenerative disorder of the central nervous system, particularly prevalent among the elderly, with its increasing incidence with age, involving multiple genetic, environmental, and lifestyle factors [83,84]. Ag-

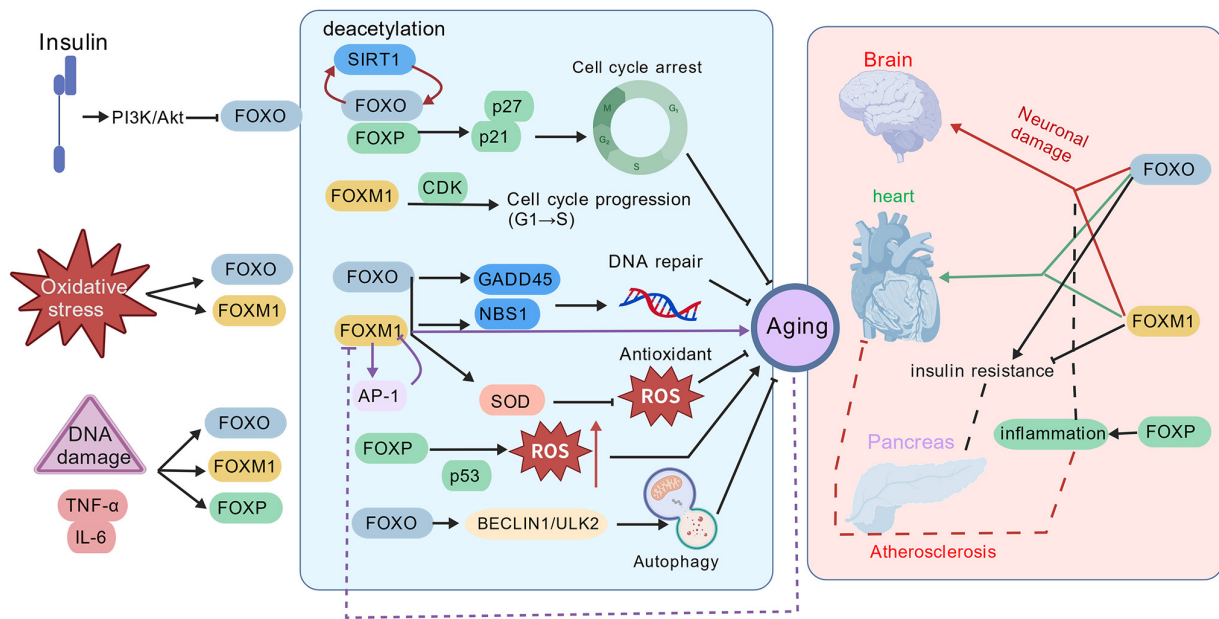


Fig. 6. The FOX family: key regulators in aging-related pathways (by BioGDP). This schematic integrates FOXO, FOXM1, and FOXP subfamilies into a dynamic regulatory network that controls cellular senescence. (1) Extracellular signals (insulin, stress, inflammation) and the intracellular transducers (PI3K/Akt, ROS, DNA damage) converge on FOX factors. (2) FOXO mainly induces cell cycle arrest, antioxidant defense, DNA repair, and autophagy. FOXM1 primarily promotes cell cycle progression, DNA repair, and suppresses senescence. FOXP cooperates with p53/p21 to induce senescence. (3) Decreased FOXO protective activity and FOXM1-induced neuronal damage, along with FOXP3-linked neuroinflammation, can accelerate Alzheimer's disease (AD) and Parkinson's disease (PD). Cardiovascular diseases: loss of FOXO cardioprotection is only partially compensated by FOXM1-mediated vascular repair, whereas Treg dysfunction indirectly promotes atherosclerosis. Metabolic diseases: FOXO decline drives insulin resistance, whereas FOXM1 improves insulin sensitivity; FOXP3+ Treg dysfunction exacerbates metabolic inflammation.

ing is a primary risk factor for PD, but the relationship is complex. During aging, diminished cellular antioxidant capacity, impaired mitochondrial function, and reduced protein clearance efficiency may increase neuronal vulnerability to damage, which promotes PD development [85]. Studies in cell lines and animal models of PD have demonstrated that abnormal FOXM1 expression correlates with the progression [86]. Specificity Protein 1 (*SPI1*), as an upstream transcription factor, can up-regulate FOXM1 expression. This up-regulation promotes the expression of Snail Family Transcriptional Repressor 2 (*SNAIL2*) and C-X-C Motif Chemokine Ligand 12 (*CXCL12*), accelerating dopaminergic neuronal damage and worsening the symptoms of patients. Mitochondrial dysfunction also exacerbates oxidative stress, damaging proteins, lipids, and DNA, thereby worsening PD progression [53]. FOXM1 regulates mitochondrial-encoded respiratory chain complex genes, such as Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 1 (*mt-ND1*) and Mitochondrially Encoded Cytochrome C Oxidase I (*mt-COI*) [87,88]. This regulation influences mitochondrial biogenesis and function, offering a potential approach to alleviate mitochondrial dysfunction and mitigate symptoms in patients with PD.

FOXO3 is predominantly protective in neurons by enhancing mitophagy, while FOXM1 exerts detrimental effects specifically in dopaminergic neurons under oxidative stress but may be protective in astrocytes.

3.2 Cardiovascular Diseases

With advancing age, the structure and function of the cardiovascular system will gradually deteriorate, leading to a significant increase in the incidence of atherosclerosis, myocardial infarction, and heart failure [89,90]. FOXO1 exerts dual effects in the cardiovascular system and provides cardioprotection by suppressing myocardial hypertrophy and fibrosis, which is achieved by regulating antioxidant enzymes and activating cell cycle inhibitors like p21 and p27 [49]. However, under specific pathological conditions, excessive FOXO1 activation may induce cardiomyocyte apoptosis and exacerbate damage in ischemic heart disease [91]. FOXO3a mitigates ischemia-reperfusion injury by suppressing oxidative stress and cardiomyocyte apoptosis, and acts by activating antioxidant and autophagy-related genes. Furthermore, in cultured vascular smooth muscle cells and animal models, FOXM1 promotes vascular remodeling by regulating cell proliferation and migration [50].

In the heart, FOXO1 and FOXO3a exert protective roles mainly in cardiomyocytes by reducing hypertrophy and apoptosis, whereas FOXM1 promotes proliferation and migration primarily in vascular smooth muscle cells and endothelial cells, contributing to vascular remodeling.

3.3 Metabolic Disorders

Metabolic disorders are significant for the incidence, which is increasing markedly with advancing age. Diabetes is a prominent example, and the prevalence is closely linked to population aging [92,93].

Changes in dietary patterns and increased human lifespan have led to a surge in elderly diabetes patients. The prevalence of diabetes increases markedly with aging [94,95]. Aging and diabetes exhibit bidirectional interaction. Diabetes accelerates aging, and aging is a significant factor in diabetes onset and progression. The glucolipotoxic microenvironment in type 2 diabetes accelerates cell aging and senescence. Conversely, cell senescence promotes the progression of type 2 diabetes [96]. For instance, senescence of pancreatic β -cells leads to functional impairment. Senescent adipocytes trigger pro-inflammatory cytokine secretion, disrupting lipid metabolism and exacerbating insulin resistance. Senescence in vascular endothelial cells and other tissues also contributes to chronic diabetic complications.

FOX family of transcription factors influences diabetes onset, progression, and complications. This family plays a pivotal role in type 2 diabetes pathogenesis [97]. It participates in insulin resistance, pancreatic β -cell function, apoptosis, and obesity-related processes. FOXO protein is primarily expressed in adult pancreatic β -cells. The activity is regulated by post-translational modifications, such as phosphorylation, acetylation, and ubiquitination. FOXO1 expression levels are negatively correlated with cellular insulin sensitivity. Regarding β -cell function, FOXO1 influences the proliferation, differentiation, and apoptosis by regulating genes such as Neurogenin-3 (*NGN3*) and NK6 Homeobox 1 (*NKX6-1*) [98]. FOXM1 modulation improves insulin resistance and secretion. Research indicates that FOXM1 inhibition in diabetic mouse models delays wound healing and reduces the recruitment of neutrophils and macrophages to diabetic wounds [51,52]. Diabetic foot ulcers (DFUs) associated with high mortality, severely impact patients' quality of life. In diabetic mouse models, FOXM1 deficiency may lead to reduced neutrophil counts, compromising the immune response and contributing to DFUs, which is compounded by the role of FOXM1 in regulating neutrophil ROS levels. FOXM1 inhibition increases ROS, further promoting DFUs development.

In metabolic tissues, FOXO1 regulates insulin sensitivity mainly in hepatocytes and adipocytes, whereas FOXM1 primarily influences the function of immune cells such as neutrophils to regulate diabetic wound healing.

Research indicates that FOX members function by directly regulating key pathways, including cell cycle progression, oxidative stress response, DNA repair, and metabolic homeostasis. These actions contribute substantially to the pathogenesis of multiple aging-related diseases. Thus, intervention strategies targeting FOX pathway could offer a novel therapeutic direction to simultaneously mitigate various aging-related pathological phenotypes and provide a theoretical foundation for translational applications. The specific roles of FOX family in neurodegenerative, cardiovascular, and metabolic diseases can be illustrated in Fig. 5.

Despite of the distinct pathological features of neurodegenerative, cardiovascular, and metabolic diseases, FOX members also operate through shared molecular pathways while exhibiting disease-specific effects. FOXO1 and FOXO3 consistently exert protective functions across all the three disease categories by enhancing autophagy, promoting antioxidant defenses, and facilitating DNA repair [99,100]. In contrast to FOXO, FOXM1 displays striking context dependency. FOXM1 protects against cardiac ischemia-reperfusion injury and promotes vascular repair [101], yet it exacerbates neuronal damage under acute oxidative stress in PD [53]. This dualism reflects differences in cell-type-specific signaling environments and underscores the need for disease-tailored interventions. FOXp3, primarily known for its role in regulatory T cells, links immunosenescence to both neuroinflammation and metabolic inflammation [54,55]. While its direct involvement in cardiovascular disease is less pronounced, chronic low-grade inflammation driven by Treg dysfunction contributes indirectly to atherosclerosis [56]. Therefore, clinical trials targeting FOX members in age-related diseases are urgently needed to bridge the gap between bench and bedside [60,62]. For instance, the FOXO4-p53 axis has emerged as a senolytic target [61]. The peptide FOXO4-DRI disrupts this interaction, reducing senescent cell burden and improving cognitive function in aged models. Clinically, dasatinib plus quercetin (D+Q) has completed Phase 1 trials in mild AD, demonstrating CNS penetration, reduced inflammation, and early cognitive signals [102]. Importantly, combining D+Q with a FOXM1 inhibitor (targeting the PGAM1-Chk1-FOXM1 axis) may achieve synergistic senolysis. FOXM1 inhibition sensitizes senescent cells, while D+Q clears residual cells via broad anti-apoptotic pathways [63]. Such dual-mechanism strategies represent a promising direction for clinical translation.

4. Conclusion and Future Perspectives

The mechanism by which FOX family influences aging is complex and multidimensional. FOXO significantly impacts cellular aging processes through multiple pathways, including cell cycle arrest, resistance to oxidative stress, promotion of DNA repair, and regulation of autophagy. It has demonstrated potential effects in delaying

aging progression across various biological models. Conversely, FOXM1 indirectly influences aging by maintaining cellular proliferative capacity through fine-tuned regulation of cell cycle progression and resistance to oxidative stress. FOXF regulates cell cycle arrest and apoptosis through interactions with the p53 signaling pathway, thereby further participating in the regulation of cellular senescence. These findings not only reveal the potential value of FOX family in delaying aging, but also lay a theoretical foundation for developing therapeutic strategies against aging-related diseases, further highlighting the central role of FOX family in aging-related pathological processes. All above is illustrated in Fig. 6.

Despite modulating the expression and activity of FOX members offers potential avenues for influencing the aging process, regulating age-related diseases, and extending lifespan, the precise function of FOX members across different cell types and tissues, the regulatory mechanisms and synergistic roles in aging and disease warrant further investigation. Small-molecular FOXM1 inhibitors and FOXO activators have been developed; the specificity, *in vivo* efficacy, and safety in aging contexts require rigorous validation. Future research should prioritize the development of tissue-specific delivery systems or intermittent dosing regimens to avoid oncogenic side effects.

Author Contributions

ZZ: Conceptualization, Writing – review & editing. JL: Conceptualization, Writing – original draft, Visualization, Writing – review & editing. YY: Visualization, Writing – review & editing. SH: Investigation, Writing – review & editing. XGL: Investigation, Writing – review & editing. XL: Investigation, Writing – review & editing. JT: Conceptualization, Writing – original draft, Supervision, Writing – review & editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The authors would like to sincerely thank the anonymous reviewers for their time, insightful comments, and valuable suggestions.

Funding

This paper is funded by grants from Guangxi Natural Science Foundation (2023GXNSFAA026390, 2023GXNSFAA026131) and the National Natural Science Foundation of China (82560721).

Conflicts of Interest

The authors declare no conflicts of interest.

References

- [1] Guo J, Huang X, Dou L, Yan M, Shen T, Tang W, et al. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. *Signal Transduction and Targeted Therapy*. 2022; 7: 391. <https://doi.org/10.1038/s41392-022-01251-0>
- [2] Milosic F, Hengstschlager M, Osmanagic-Myers S. Premature aging in genetic diseases: what conclusions can be drawn for physiological aging. *Frontiers in Aging*. 2024; 4: 1327833. <http://doi.org/10.3389/fragi.2023.1327833>
- [3] Magkouta S, Veroutis D, Papaspyropoulos A, Georgiou M, Lougiakis N, Pippa N, et al. Generation of a selective senolytic platform using a micelle-encapsulated Sudan Black B conjugated analog. *Nature Aging*. 2025; 5: 162–175. <https://doi.org/10.1038/s43587-024-00747-4>
- [4] Aguado J, Amarilla AA, Taherian Fard A, Albornoz EA, Tyshkovskiy A, Schwabenland M, et al. Senolytic therapy alleviates physiological human brain aging and COVID-19 neuropathology. *Nature Aging*. 2023; 3: 1561–1575. <https://doi.org/10.1038/s43587-023-00519-6>
- [5] Chen MS, Lee RT, Garbern JC. Senescence mechanisms and targets in the heart. *Cardiovascular Research*. 2022; 118: 1173–1187. <https://doi.org/10.1093/cvr/cvab161>
- [6] Moskalev AA, Shaposhnikov MV, Plyusnina EN, Zhavoronkov A, Budovsky A, Yanai H, et al. The role of DNA damage and repair in aging through the prism of Koch-like criteria. *Ageing Research Reviews*. 2013; 12: 661–684. <https://doi.org/10.1016/j.arr.2012.02.001>
- [7] Gulen MF, Samson N, Keller A, Schwabenland M, Liu C, Glück S, et al. cGAS-STING drives ageing-related inflammation and neurodegeneration. *Nature*. 2023; 620: 374–380. <https://doi.org/10.1038/s41586-023-06373-1>
- [8] Yousefzadeh MJ, Flores RR, Zhu Y, Schmiechen ZC, Brooks RW, Trussoni CE, et al. An aged immune system drives senescence and ageing of solid organs. *Nature*. 2021; 594: 100–105. <https://doi.org/10.1038/s41586-021-03547-7>
- [9] Castaneda M, Hollander PD, Mani SA. Forkhead Box Transcription Factors: Double-Edged Swords in Cancer. *Cancer Research*. 2022; 82: 2057–2065. <https://doi.org/10.1158/0008-5472.CAN-21-3371>
- [10] Jin Y, Liang Z, Lou H. The Emerging Roles of Fox Family Transcription Factors in Chromosome Replication, Organization, and Genome Stability. *Cells*. 2020; 9: 258. <https://doi.org/10.3390/cells9010258>
- [11] Liu YQ, Zhou ZG, Yang M, Wang YX, Qin YF, Tu J. Research progress of FOX family promotion for liver fibrosis. *Acta Medicinæ Sinica*. 2023; 36: 170–174. <https://doi.org/10.19296/j.cnki.1008-2409.2023-033> (In Chinese)
- [12] Ma X, Lin Y, Zhang L, Huang Z, Zhang Y, Fu X, et al. The dual missions of FoxO3a in inflammatory diseases: Regulation of antioxidant enzymes and involvement in programmed cell death. *International Immunopharmacology*. 2025; 151: 114369. <https://doi.org/10.1016/j.intimp.2025.114369>
- [13] Timilsina S, Huang JY, Abdelfattah N, Medina D, Singh D, Abdulsahib S, et al. Epigenetic silencing of DNA sensing pathway by FOXM1 blocks stress ligand-dependent antitumor immunity and immune memory. *Nature Communications*. 2025; 16: 3967. <https://doi.org/10.1038/s41467-025-59186-3>
- [14] Zhang Z, Li M, Sun T, Zhang Z, Liu C. FOXM1: Functional Roles of FOXM1 in Non-Malignant Diseases. *Biomolecules*. 2023; 13: 857. <https://doi.org/10.3390/biom13050857>
- [15] Dolsten GA, Pritykin Y. Genomic Analysis of Foxp3 Function in Regulatory T Cells. *Journal of Immunology (Baltimore, Md.: 1950)*. 2023; 210: 880–887. <https://doi.org/10.4049/jimmunol>

- [16] Jiramongkol Y, Lam EWF. FOXO transcription factor family in cancer and metastasis. *Cancer Metastasis Reviews*. 2020; 39: 681–709. <https://doi.org/10.1007/s10555-020-09883-w>
- [17] Natarajan SR, Krishnamoorthy R, Alshuniaber MA, Al-Anazi KM, Farah MA, Rajagopal P, et al. Identification of FOXM1 as a novel protein biomarker and therapeutic target for colorectal cancer progression: Evidence from immune infiltration and bioinformatic analyses. *International Journal of Biological Macromolecules*. 2024; 282: 137201. <https://doi.org/10.1016/j.ijbiomac.2024.137201>
- [18] Yang Y, Zhao P, Chen H, Tu Y, Zhou Y, Liu X, et al. Novel Strategies against Hepatocellular Carcinoma through Lipid Metabolism. *Oncology Research*. 2025; 33: 3247–3268. <https://doi.org/10.32604/or.2025.066440>
- [19] Rokavec M, Du Y, Hermeking H. Down-regulation of RBM47 due to diminished activation by forkhead box A1 (FOXA1) and silencing by CpG methylation is associated with epithelial-mesenchymal transition and metastasis of colorectal cancer. *Molecular Biomedicine*. 2025; 6: 133. <https://doi.org/10.1186/s43556-025-00382-4>
- [20] Ribeiro R, Macedo JC, Costa M, Ustiyana V, Shindyapina AV, Tyshkovskiy A, et al. In vivo cyclic induction of the FOXM1 transcription factor delays natural and progeroid aging phenotypes and extends healthspan. *Nature Aging*. 2022; 2: 397–411. <https://doi.org/10.1038/s43587-022-00209-9>
- [21] Chang ZS, He ZM, Xia JB. FoxO3 Regulates the Progress and Development of Aging and Aging-Related Diseases. *Current Molecular Medicine*. 2023; 23: 991–1006. <https://doi.org/10.2174/1566524023666221014140817>
- [22] Oda JMM, Hirata BKB, Guembarovski RL, Watanabe MAE. Genetic polymorphism in FOXP3 gene: imbalance in regulatory T-cell role and development of human diseases. *Journal of Genetics*. 2013; 92: 163–171. <https://doi.org/10.1007/s12041-013-0213-7>
- [23] Zhang T, Liu S, Durojaye O, Xiong F, Fang Z, Ullah T, et al. Dynamic phosphorylation of FOXA1 by Aurora B guides post-mitotic gene reactivation. *Cell Reports*. 2024; 43: 114739. <https://doi.org/10.1016/j.celrep.2024.114739>
- [24] Zhu J, Wei Y, Deng F, Zhou Y, Yang Z, Ma Y. The Role of FOXA1 in Human Normal Development and Its Functions in Sex Hormone-Related Cancers. *Frontiers in Bioscience (Landmark Edition)*. 2024; 29: 225. <https://doi.org/10.31083/j.fb12906225>
- [25] Lin W, Tang Y, Zhao Y, Zhao J, Zhang L, Wei W, et al. MiR-144-3p Targets FoxO1 to Reduce Its Regulation of Adiponectin and Promote Adipogenesis. *Frontiers in Genetics*. 2020; 11: 603144. <https://doi.org/10.3389/fgene.2020.603144>
- [26] Mu Q, Miao L, Qian L, Lin Y, Jiang W, Ge X. Regulation of sirt1 and foxO1 in glucose metabolism of Megalobrama amblycephala. *Gene*. 2024; 903: 148172. <https://doi.org/10.1016/j.gene.2024.148172>
- [27] Hu Z, Chen D, Yan P, Zheng F, Zhu H, Yuan Z, et al. Puerarin suppresses macrophage M1 polarization to alleviate renal inflammatory injury through antagonizing TLR4/MyD88-mediated NF- κ B p65 and JNK/FoxO1 activation. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*. 2024; 132: 155813. <https://doi.org/10.1016/j.phymed.2024.155813>
- [28] Farhan M, Silva M, Xingan X, Huang Y, Zheng W. Role of FOXO Transcription Factors in Cancer Metabolism and Angiogenesis. *Cells*. 2020; 9: 1586. <https://doi.org/10.3390/cell9071586>
- [29] Kuo CJ, Manastireanu DM, Nieto-Torres JL, Kumsta C. Transcriptional Dysregulation of Autophagy in Aging and Potential Interventions: Insights Into TFEB and FOXOs. *Frontiers in Bioscience (Landmark Edition)*. 2025; 30: 38730. <https://doi.org/10.31083/FBL38730>
- [30] Tao J, Xu XS, Song YZ, Qu K, Wu QF, Wang RT, et al. Down-regulation of FoxM1 inhibits viability and invasion of gallbladder carcinoma cells, partially dependent on induction of cellular senescence. *World Journal of Gastroenterology*. 2014; 20: 9497–9505. <https://doi.org/10.3748/wjg.v20.i28.9497>
- [31] Wang X, Sun J, Cui M, Zhao F, Ge C, Chen T, et al. Down-regulation of FOXP1 Inhibits Cell Proliferation in Hepatocellular Carcinoma by Inducing G1/S Phase Cell Cycle Arrest. *International Journal of Molecular Sciences*. 2016; 17: 1501. <https://doi.org/10.3390/ijms17091501>
- [32] Yu C, Li X, Zhao Y, Hu Y. The role of FOXA family transcription factors in glucolipid metabolism and NAFLD. *Frontiers in Endocrinology*. 2023; 14: 1081500. <https://doi.org/10.3389/fendo.2023.1081500>
- [33] Cao G, Lin M, Gu W, Su Z, Duan Y, Song W, et al. The rules and regulatory mechanisms of FOXO3 on inflammation, metabolism, cell death and aging in hosts. *Life Sciences*. 2023; 328: 121877. <https://doi.org/10.1016/j.lfs.2023.121877>
- [34] Ferreira FJ, Galhardo M, Nogueira JM, Teixeira J, Logarinho E, Bessa J. FOXM1 expression reverts aging chromatin profiles through repression of the senescence-associated pioneer factor AP-1. *Nature Communications*. 2025; 16: 2931. <https://doi.org/10.1038/s41467-025-57503-4>
- [35] Hlavac K, Pavelkova P, Ondrisova L, Mraz M. FoxO1 signaling in B cell malignancies and its therapeutic targeting. *FEBS Letters*. 2025; 599: 2911–2931. <https://doi.org/10.1002/1873-3468.15057>
- [36] Palomer X, Salvador JM, Griñán-Ferré C, Barroso E, Pallàs M, Vázquez-Carrera M. GADD45A: With or without you. *Medicinal Research Reviews*. 2024; 44: 1375–1403. <https://doi.org/10.1002/med.22015>
- [37] Huang X, Zhang X, Machireddy N, Evans CE, Trewartha SD, Hu G, et al. Endothelial FoxM1 reactivates aging-impaired endothelial regeneration for vascular repair and resolution of inflammatory lung injury. *Science Translational Medicine*. 2023; 15: eabm5755. <https://doi.org/10.1126/scitranslmed.abm5755>
- [38] Chand V, Liao X, Guzman G, Benevolenskaya E, Raychaudhuri P. Hepatocellular carcinoma evades RB1-induced senescence by activating the FOXM1-FOXO1 axis. *Oncogene*. 2022; 41: 3778–3790. <https://doi.org/10.1038/s41388-022-02394-8>
- [39] Khongkow P, Karunaratna U, Khongkow M, Gong C, Gomes AR, Yagüe E, et al. FOXM1 targets NBS1 to regulate DNA damage-induced senescence and epirubicin resistance. *Oncogene*. 2014; 33: 4144–4155. <https://doi.org/10.1038/onc.2013.457>
- [40] Kim JE, Shin JS, Moon JH, Hong SW, Jung DJ, Kim JH, et al. Foxp3 is a key downstream regulator of p53-mediated cellular senescence. *Oncogene*. 2017; 36: 219–230. <https://doi.org/10.1038/onc.2016.193>
- [41] Yang L, Han X, Wang M, Zhang X, Wang L, Xu N, et al. Early Growth Response Gene 1 Benefits Autoimmune Disease by Promoting Regulatory T Cell Differentiation as a Regulator of Foxp3. *Research (Washington, D.C.)*. 2025; 8: 0662. <https://doi.org/10.34133/research.0662>
- [42] Thangavelu L, Altamimi ASA, Ghaboura N, Babu MA, Roopashree R, Sharma P, et al. Targeting the p53-p21 axis in liver cancer: Linking cellular senescence to tumor suppression and progression. *Pathology, Research and Practice*. 2024; 263: 155652. <https://doi.org/10.1016/j.prp.2024.155652>
- [43] Ochodnicka-Mackovicova K, van Keimpema M, Spaargaren M, van Noesel CJM, Guikema JEJ. DNA damage-induced p53 downregulates expression of RAG1 through a negative feedback loop involving miR-34a and FOXP1. *The Journal of Biological Chemistry*. 2024; 300: 107922. <https://doi.org/10.1016/j.jbc.2024.107922>
- [44] Li Q, Zhang Y, Fu J, Han L, Xue L, Lv C, et al. FOXA1 mediates p16(INK4a) activation during cellular senescence. *The*

- EMBO Journal. 2013; 32: 858–873. <https://doi.org/10.1038/emboj.2013.35>
- [45] Sheaffer KL, Updike DL, Mango SE. The Target of Rapamycin pathway antagonizes pha-4/FoxA to control development and aging. *Current Biology: CB*. 2008; 18: 1355–1364. <https://doi.org/10.1016/j.cub.2008.07.097>
- [46] Li B, Xiong W, Zuo W, Shi Y, Wang T, Chang L, et al. Proximal telomeric decompaction due to telomere shortening drives FOXO1-dependent myocardial senescence. *Nucleic Acids Research*. 2024; 52: 6269–6284. <https://doi.org/10.1093/nar/gkac274>
- [47] Kousa AI, Jahn L, Zhao K, Flores AE, Acenas D, 2nd, Lederer E, et al. Age-related epithelial defects limit thymic function and regeneration. *Nature Immunology*. 2024; 25: 1593–1606. <https://doi.org/10.1038/s41590-024-01915-9>
- [48] Hu M, Kang X, Liu Z, Wang S, Liu S, Li C, et al. Senescent-like border-associated macrophages regulate cognitive aging via migrasome-mediated induction of paracrine senescence in microglia. *Nature Aging*. 2025; 5: 2039–2054. <https://doi.org/10.1038/s43587-025-00956-5>
- [49] Townsend N, Timmis A, Erglis A, Miličić D, Perrone-Filardi P, Weidinger F, et al. Challenges in the prevention, treatment and management of cardiovascular disease among older adults. *The Lancet Regional Health. Europe*. 2025; 56: 101372. <https://doi.org/10.1016/j.lanepe.2025.101372>
- [50] Grobs Y, Romanet C, Lemay SE, Bourgeois A, Voisine P, Theberge C, et al. ATP citrate lyase drives vascular remodeling in systemic and pulmonary vascular diseases through metabolic and epigenetic changes. *Science Translational Medicine*. 2024; 16: eado7824. <https://doi.org/10.1126/scitranslmed.ado7824>
- [51] Marchelek-Mysliwiec M, Nalewajska M, Turoń-Skrzypińska A, Kotrych K, Dziedzicko V, Sulikowski T, et al. The Role of Forkhead Box O in Pathogenesis and Therapy of Diabetes Mellitus. *International Journal of Molecular Sciences*. 2022; 23: 11611. <https://doi.org/10.3390/ijms231911611>
- [52] Sawaya AP, Stone RC, Brooks SR, Pastar I, Jozic I, Hasneen K, et al. Deregulated immune cell recruitment orchestrated by FOXM1 impairs human diabetic wound healing. *Nature Communications*. 2020; 11: 4678. <https://doi.org/10.1038/s41467-020-18276-0>
- [53] Dong L, Gao L. SP1-Driven FOXM1 Upregulation Induces Dopaminergic Neuron Injury in Parkinson's Disease. *Molecular Neurobiology*. 2024; 61: 5510–5524. <https://doi.org/10.1007/s12035-023-03854-2>
- [54] Yang KY, Liao J, Ma Z, Tse HF, Lu L, Graca L, et al. Single-cell transcriptomics of Treg reveals hallmarks and trajectories of immunological aging. *Journal of Leukocyte Biology*. 2024; 115: 19–35. <https://doi.org/10.1093/jleuko/qiad104>
- [55] Petakh P, Kamyshna I, Oksenysh V, Kamyshnyi O. Metformin Alters mRNA Expression of *FOXP3*, *RORC*, and *TBX21* and Modulates Gut Microbiota in COVID-19 Patients with Type 2 Diabetes. *Viruses*. 2024; 16: 281. <https://doi.org/10.3390/v16020281>
- [56] Kologrivova IV, Dmitriukov AA, Naryzhnaya NV, Kravchenko ES, Kharitonova OA, Vyrostkova AI, et al. Production of the Key Immunoregulatory Cytokines and the Content of FoxP3⁺ T-Regulatory Lymphocytes in the Epicardial and Thymus Adipose Tissue in Patients with Coronary Heart Disease. *Bulletin of Experimental Biology and Medicine*. 2024; 178: 184–188. <https://doi.org/10.1007/s10517-025-06304-2>
- [57] Wang L, Zhai D, Tang L, Zhang H, Wang X, Ma N, et al. FOXM1 mediates methotrexate resistance in osteosarcoma cells by promoting autophagy. *Acta Biochimica et Biophysica Sinica*. 2024; 56: 1289–1299. <https://doi.org/10.3724/abbs.2024084>
- [58] Zhang Y, Ding N, Li Y, Ouyang M, Fu P, Peng Y, et al. Transcription factor FOXM1 specifies chromatin DNA to extracellular vesicles. *Autophagy*. 2024; 20: 1054–1071. <https://doi.org/10.1080/15548627.2023.2284523>
- [59] Wu D, Xu Q, Wu S, Tan J, Khan FA, Pandupuspitasari NS, et al. Pursuing healthy aging and longevity through natural product and stem cell-driven rejuvenation. *Biochemical Pharmacology*. 2025; 242: 117359. <https://doi.org/10.1016/j.bcp.2025.117359>
- [60] McIntyre RL, Liu YJ, Hu M, Morris BJ, Willcox BJ, Donlon TA, et al. Pharmaceutical and nutraceutical activation of FOXO3 for healthy longevity. *Ageing Research Reviews*. 2022; 78: 101621. <https://doi.org/10.1016/j.arr.2022.101621>
- [61] Alameen AAM, Al-Kuraishy HM, Fawzy MN, Batiha GES. Targeting the FOXO4-p53 axis by retro-inverso peptide senolytic agents: a pharmacological strategy to mitigate brain aging and cognitive decline. *Naunyn-Schmiedeberg's Archives of Pharmacology*. 2026. <https://doi.org/10.1007/s00210-026-05309-6>
- [62] Merjaneh N, Hajjar M, Lan YW, Kalinichenko VV, Kalin TV. The Promise of Combination Therapies with FOXM1 Inhibitors for Cancer Treatment. *Cancers*. 2024; 16: 756. <https://doi.org/10.3390/cancers16040756>
- [63] Mikawa T, Kameda M, Ikari S, Shibata E, Liu S, Miyagawa S, et al. Abrogation of aberrant glycolytic interactions eliminates senescent cells and alleviates aging-related dysfunctions. *Signal Transduction and Targeted Therapy*. 2025; 10: 402. <https://doi.org/10.1038/s41392-025-02502-6>
- [64] Tian XY, Zhu B, Zhou XB, Fang WC, Lei Y, Liu MN, et al. FKBP5 Regulates Osteogenesis of Human iPSC-Derived Mesenchymal Stem Cells via FKBP5-AKT-FOXO1 Pathway. *Journal of Cellular and Molecular Medicine*. 2025; 29: e70849. <https://doi.org/10.1111/jcmm.70849>
- [65] Chandramouly G. Gadd45 in DNA Demethylation and DNA Repair. *Advances in Experimental Medicine and Biology*. 2022; 1360: 55–67. https://doi.org/10.1007/978-3-030-94804-7_4
- [66] Huang Z, Jiang C, Gu J, Uvizi M, Power S, Douglas D, et al. Duplications of Human Longevity-Associated Genes Across Placental Mammals. *Genome Biology and Evolution*. 2023; 15: ead186. <https://doi.org/10.1093/gbe/evad186>
- [67] Ouchi Y, Sahu SK, Izpisua Belmonte JC. FOXM1 delays senescence and extends lifespan. *Nature Aging*. 2022; 2: 373–374. <https://doi.org/10.1038/s43587-022-00222-y>
- [68] Liu X, Zhang Y, Wang H, Li J, Chen S, Zhao L, et al. Age related decline of Cdh1 contributes to proliferative arrest and senescence in human fibroblasts. *Aging Cell*. 2023; 22: e13901. <https://doi.org/10.1111/ace1.13901>
- [69] Laoukili J, Alvarez-Fernandez M, Stahl M, Medema RH. FoxM1 is degraded at mitotic exit in a Cdh1-dependent manner. *Cell Cycle (Georgetown, Tex.)*. 2008; 7: 2720–2726. <https://doi.org/10.4161/cc.7.17.6580>
- [70] Kumari R, Hummerich H, Shen X, Fischer M, Litovchick L, Mittnacht S, et al. Simultaneous expression of MMB-FOXM1 complex components enables efficient bypass of senescence. *Scientific Reports*. 2021; 11: 21506. <https://doi.org/10.1038/s41598-021-01012-z>
- [71] Durojaye OA, Yekkeen AA, Idris MO, Okoro NO, Odiba AS, Nwanguma BC. Investigation of the MDM2-binding potential of de novo designed peptides using enhanced sampling simulations. *International Journal of Biological Macromolecules*. 2024; 269: 131840. <https://doi.org/10.1016/j.ijbiomac.2024.131840>
- [72] Li H, Liu P, Xu S, Li Y, Dekker JD, Li B, et al. FOXP1 controls mesenchymal stem cell commitment and senescence during skeletal aging. *The Journal of Clinical Investigation*. 2025; 135: e191424. <https://doi.org/10.1172/JCI191424>
- [73] He R, Xiao C, Lei W, Chen G, Li Y, Luo OJ. Aging-associated transcriptional programs in T cells signify constituents of TGF-β signaling for immunosenescence. *BMC Biology*. 2025; 24: 17. <https://doi.org/10.1186/s12915-025-02484-5>
- [74] Xia K, Huang W, Zhao X, Huang X, Chen Y, Yu L, et al. Increased FOXA1 levels induce apoptosis and inhibit proliferation in FOXA1-low expressing basal breast cancer cells. *American*

Journal of Cancer Research. 2022; 12: 2641–2658.

- [75] Baker DJ, Petersen RC. Cellular senescence in brain aging and neurodegenerative diseases: evidence and perspectives. *The Journal of Clinical Investigation*. 2018; 128: 1208–1216. <https://doi.org/10.1172/JCI95145>
- [76] Carr L, Mustafa S, Collins-Praino LE. The Hallmarks of Ageing in Microglia. *Cellular and Molecular Neurobiology*. 2025; 45: 45. <https://doi.org/10.1007/s10571-025-01564-y>
- [77] Li K, Qiu X, Yang Q, Wang Z. Histone modifications: Key players in Alzheimer's disease. *Mechanisms of Ageing and Development*. 2025; 228: 112102. <https://doi.org/10.1016/j.mad.2025.112102>
- [78] Di Rienzo M, Romagnoli A, Refolo G, Vescovo T, Ciccocanti F, Zuchegna C, et al. Role of AMBRA1 in mitophagy regulation: emerging evidence in aging-related diseases. *Autophagy*. 2024; 20: 2602–2615. <https://doi.org/10.1080/15548627.2024.2389474>
- [79] Rai SN, Singh C, Singh A, Singh MP, Singh BK. Mitochondrial Dysfunction: a Potential Therapeutic Target to Treat Alzheimer's Disease. *Molecular Neurobiology*. 2020; 57: 3075–3088. <https://doi.org/10.1007/s12035-020-01945-y>
- [80] Fang EF, Hou Y, Palikaras K, Adriaanse BA, Kerr JS, Yang B, et al. Mitophagy inhibits amyloid- β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nature Neuroscience*. 2019; 22: 401–412. <https://doi.org/10.1038/s41593-018-0332-9>
- [81] Song YM, Lee YH, Kim JW, Ham DS, Kang ES, Cha BS, et al. Metformin alleviates hepatosteatosis by restoring SIRT1-mediated autophagy induction via an AMP-activated protein kinase-independent pathway. *Autophagy*. 2015; 11: 46–59. <https://doi.org/10.4161/15548627.2014.984271>
- [82] Bofill-De Ros X, Santos M, Vila-Casadesús M, Villanueva E, Andreu N, Dierssen M, et al. Genome-wide miR-155 and miR-802 target gene identification in the hippocampus of Ts65Dn Down syndrome mouse model by miRNA sponges. *BMC Genomics*. 2015; 16: 907. <https://doi.org/10.1186/s12864-015-2160-6>
- [83] Tsalenchuk M, Gentleman SM, Marzi SJ. Linking environmental risk factors with epigenetic mechanisms in Parkinson's disease. *NPJ Parkinson's Disease*. 2023; 9: 123. <https://doi.org/10.1038/s41531-023-00568-z>
- [84] Chaudhary JK, Danga AK, Kumari A, Bhardwaj A, Rath PC. Role of chemokines in aging and age-related diseases. *Mechanisms of Ageing and Development*. 2025; 223: 112009. <https://doi.org/10.1016/j.mad.2024.112009>
- [85] Ngana GS, Di Bernardo MA, Surette MG, MacNeil LT. *Actinomyces viscosus* promotes neuroprotection in *C. elegans* models of Parkinson's disease. *Mechanisms of Ageing and Development*. 2025; 225: 112061. <https://doi.org/10.1016/j.mad.2025.112061>
- [86] Brooker SM, Naylor GE, Krainc D. Cell biology of Parkinson's disease: Mechanisms of synaptic, lysosomal, and mitochondrial dysfunction. *Current Opinion in Neurobiology*. 2024; 85: 102841. <https://doi.org/10.1016/j.conb.2024.102841>
- [87] Cheng Y, Sun F, Thornton K, Jing X, Dong J, Yun G, et al. FOXM1 regulates glycolysis and energy production in multiple myeloma. *Oncogene*. 2022; 41: 3899–3911. <https://doi.org/10.1038/s41388-022-02398-4>
- [88] Kobiita A, Silva PN, Schmid MW, Stoffel M. FoxM1 coordinates cell division, protein synthesis, and mitochondrial activity in a subset of β cells during acute metabolic stress. *Cell Reports*. 2023; 42: 112986. <https://doi.org/10.1016/j.celrep.2023.112986>
- [89] Zhao D, Wang Y, Wong ND, Wang J. Impact of Aging on Cardiovascular Diseases: From Chronological Observation to Biological Insights: *JACC Family Series*. *JACC. Asia*. 2024; 4: 345–358. <https://doi.org/10.1016/j.jacasi.2024.02.002>
- [90] Javadifar A, Tahani M, Khayat S, Nasab SR, Karav S, Kesharwani P, et al. Targeting mitophagy in the heart: Exploring the therapeutic potential of MicroRNAs. *Mechanisms of Ageing and Development*. 2025; 226: 112082. <https://doi.org/10.1016/j.mad.2025.112082>
- [91] Wu X, Du X, Lu C. Targeting FoxO1 in cardiovascular diseases: Mechanisms and therapeutic potential. *Pharmacological Research*. 2026; 225: 108122. <https://doi.org/10.1016/j.phrs.2026.108122>
- [92] Xie M, Li X, Chen L, Zhang Y, Chen L, Hua H, et al. The crosstalks between vascular endothelial cells, vascular smooth muscle cells, and adventitial fibroblasts in vascular remodeling. *Life Sciences*. 2025; 361: 123319. <https://doi.org/10.1016/j.lfs.2024.123319>
- [93] Sinclair A, Saeedi P, Kaundal A, Karuranga S, Malanda B, Williams R. Diabetes and global ageing among 65–99-year-old adults: Findings from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*. 2020; 162: 108078. <https://doi.org/10.1016/j.diabres.2020.108078>
- [94] Gems D, de Magalhães JP. The hoverfly and the wasp: A critique of the hallmarks of aging as a paradigm. *Ageing Research Reviews*. 2021; 70: 101407. <https://doi.org/10.1016/j.arr.2021.101407>
- [95] Schafer MJ, Zhang X, Kumar A, Atkinson EJ, Zhu Y, Jachim S, et al. The senescence-associated secretome as an indicator of age and medical risk. *JCI Insight*. 2020; 5: e133668. <https://doi.org/10.1172/jci.insight.133668>
- [96] Borrás C, Abdelaziz KM, Díaz A, Gambini J, Jové M, López-Gruoso R, et al. Lifelong soya consumption in males does not increase lifespan but increases health span under a metabolic stress such as type 2 diabetes mellitus. *Mechanisms of Ageing and Development*. 2021; 200: 111596. <https://doi.org/10.1016/j.mad.2021.111596>
- [97] Parthiban NK, Nassif NT, Simpson AM. Functions and Mechanisms of Diabetes-Linked Transcription Factors. *Frontiers in Bioscience (Landmark Edition)*. 2025; 30: 36544. <https://doi.org/10.31083/fbl36544>
- [98] Pellegrino R, Perpetuini D, Paganelli R, Di Iorio A, Filoni S, Tinari N, et al. Galectin-3-binding protein is a risk factor for diabetes, metabolic syndrome, and inflammation. Cross-sectional and longitudinal results from the INCHIANTI study. *Mechanisms of Ageing and Development*. 2025; 226: 112086. <https://doi.org/10.1016/j.mad.2025.112086>
- [99] Marchetti B, Tirolo C, L'Episcopo F, Caniglia S, Testa N, Smith JA, et al. Parkinson's disease, aging and adult neurogenesis: Wnt/ β -catenin signalling as the key to unlock the mystery of endogenous brain repair. *Aging Cell*. 2020; 19: e13101. <https://doi.org/10.1111/acer.13101>
- [100] Asadi Y, Moundounga RK, Chakroborty A, Pokokiri A, Wang H. FOXOs and their roles in acute and chronic neurological disorders. *Frontiers in Molecular Biosciences*. 2025; 12: 1538472. <https://doi.org/10.3389/fmolb.2025.1538472>
- [101] Song S, Zhang X, Huang Z, Pei Z, Zeng L, Cai F, et al. FOXM1 Protects Against Myocardial Ischemia-Reperfusion Injury in Rodent and Porcine Models by Suppressing MKRN1-Dependent LKB1 Ubiquitination. *Advanced Science (Weinheim, Baden-Wurtemberg, Germany)*. 2025; 12: e08673. <https://doi.org/10.1002/adv.202508673>
- [102] Garbarino VR, Palavicini JP, Melendez J, Barthelemy NR, He Y, Kautz TF, et al. Evaluation of exploratory fluid biomarkers from a phase 1 senolytic trial in mild Alzheimer's disease. *Neurotherapeutics: the Journal of the American Society for Experimental NeuroTherapeutics*. 2025; 22: e00591. <https://doi.org/10.1016/j.neurot.2025.e00591>