



**VICTORIA UNIVERSITY**  
MELBOURNE AUSTRALIA

## *Recent advances in understanding the role of FOXO3*

This is the Published version of the following publication

Stefanetti, Renae J, Voisin, Sarah, Russell, Aaron and Lamon, Séverine  
(2018) Recent advances in understanding the role of FOXO3.  
F1000Research, 7. ISSN 2046-1402

The publisher's official version can be found at  
<https://f1000research.com/articles/7-1372/v1>

Note that access to this version may require subscription.

Downloaded from VU Research Repository <https://vuir.vu.edu.au/38231/>



## REVIEW

# Recent advances in understanding the role of FOXO3 [version 1; referees: 4 approved]

Renae J. Stefanetti <sup>1</sup>, Sarah Voisin <sup>2</sup>, Aaron Russell <sup>3</sup>, Séverine Lamon <sup>3</sup>

<sup>1</sup>Wellcome Centre for Mitochondrial Research, Newcastle University, Newcastle upon Tyne, UK

<sup>2</sup>Institute for Health and Sport, Victoria University, Footscray, Australia

<sup>3</sup>Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Geelong, Australia

**v1** First published: 31 Aug 2018, 7(F1000 Faculty Rev):1372 (doi: [10.12688/f1000research.15258.1](https://doi.org/10.12688/f1000research.15258.1))

Latest published: 31 Aug 2018, 7(F1000 Faculty Rev):1372 (doi: [10.12688/f1000research.15258.1](https://doi.org/10.12688/f1000research.15258.1))

## Abstract

The forkhead box O3 (FOXO3, or FKHL1) protein is a member of the FOXO subclass of transcription factors. FOXO proteins were originally identified as regulators of insulin-related genes; however, they are now established regulators of genes involved in vital biological processes, including substrate metabolism, protein turnover, cell survival, and cell death. FOXO3 is one of the rare genes that have been consistently linked to longevity in *in vivo* models. This review provides an update of the most recent research pertaining to the role of FOXO3 in (i) the regulation of protein turnover in skeletal muscle, the largest protein pool of the body, and (ii) the genetic basis of longevity. Finally, it examines (iii) the role of microRNAs in the regulation of FOXO3 and its impact on the regulation of the cell cycle.

## Keywords

FOXO3, transcription factor, skeletal muscle, protein turnover, longevity, microRNA

## Open Peer Review

Referee Status:

	Invited Referees			
	1	2	3	4
version 1 published 31 Aug 2018				

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

- 1 **Saghi Ghaffari**, Icahn School of Medicine at Mount Sinai, USA
- 2 **Bradley J. Willcox**, University of Hawaii, USA
- 3 **Wolfgang Link**, University of Algarve, Portugal
- 4 **Boudewijn M. T. Burgering**, University Medical Center Utrecht, Netherlands

## Discuss this article

Comments (0)

**Corresponding author:** Séverine Lamon ([severine.lamon@deakin.edu.au](mailto:severine.lamon@deakin.edu.au))

**Author roles:** **Stefanetti RJ:** Writing – Original Draft Preparation, Writing – Review & Editing; **Voisin S:** Writing – Original Draft Preparation, Writing – Review & Editing; **Russell A:** Conceptualization, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Lamon S:** Conceptualization, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

**Grant information:** The author(s) declared that no grants were involved in supporting this work.

**Copyright:** © 2018 Stefanetti RJ *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Stefanetti RJ, Voisin S, Russell A and Lamon S. **Recent advances in understanding the role of FOXO3 [version 1; referees: 4 approved]** *F1000Research* 2018, 7(F1000 Faculty Rev):1372 (doi: [10.12688/f1000research.15258.1](https://doi.org/10.12688/f1000research.15258.1))

**First published:** 31 Aug 2018, 7(F1000 Faculty Rev):1372 (doi: [10.12688/f1000research.15258.1](https://doi.org/10.12688/f1000research.15258.1))

## Introduction

The forkhead box O3 (FOXO3, or FKHL1) protein is one of about 40 forkhead box (FOX) transcription factors encoded by the mammalian genome<sup>1</sup>. FOX transcription factors are versatile proteins containing an evolutionarily conserved winged helix DNA-binding motif of about 100 residues at the N-terminal region, the forkhead (FKH) domain<sup>2–4</sup>. FOXO3 belongs to the FOXO subclass (made of FOXO1, FOXO3, FOXO4, and FOXO6), which historically is known to regulate insulin signaling (comprehensively reviewed in 5,6). Numerous regulatory processes, including phosphorylation, acetylation, ubiquitination, methylation<sup>7,8</sup>, and microRNA (miRNA) binding<sup>9</sup>, can modulate FOXO3 transcriptional activity. Of particular interest for human health, FOXO3 is under the control of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway<sup>10</sup>. In its non-phosphorylated form, FOXO3 localizes at the nucleus where it regulates gene transcription. Activation of the PI3K/Akt pathway results in the phosphorylation of FOXO3 at three conserved residues<sup>11</sup>. This usually causes its exclusion from the nucleus and stops the transcriptional activation of its target genes<sup>1,12</sup>. Phosphorylated FOXO3 therefore represents the inactive form of the protein. Through PI3K/Akt, FOXO3 mediates biological processes that are essential for health over the lifespan, including substrate metabolism, protein turnover, cell survival, and cell death<sup>11,13,14</sup>.

Our research group investigates skeletal muscle wasting and miRNA-mediated regulation. Although the involvement of FOXO3 in these processes is undeniable, these two topics have not been reviewed in the specific context of FOXO3. In addition, the role and regulation of FOXO3 in the genetics of longevity constitute a very dynamic research field, justifying the need for an updated review encompassing the research articles published over the last 3 years.

## FOXO3 and the regulation of skeletal muscle homeostasis

FOXO proteins are expressed across multiple tissues of the body but their expression level, function, and targets are tissue specific. In mice, *Foxo3* mRNA is enriched in the heart, brain, spleen, and kidney and, to a certain extent, skeletal muscle<sup>15</sup>. FOXO3 is a key player in the control of skeletal muscle protein turnover and a central effector of PI3K/Akt signaling, the main regulator of protein synthesis and degradation in the muscle<sup>16</sup>. In anabolic conditions, Akt phosphorylates FOXO3 and suppresses its transcriptional activity. FOXO3 inhibition in turn reduces the expression of the muscle-enriched members of the ubiquitin-proteasome system, atrogin-1 (FBXO32) and muscle RING finger 1 (MURF1)<sup>17</sup>, which promote muscle protein degradation. In addition, upon Akt activation, FOXO proteins may play a role in a negative feedback loop that inhibits Akt to maintain the cell homeostatic balance. In non-mammalian cells, FoxO orthologues inhibit the activity of the mechanistic target of rapamycin complex 1 (mTORC1)<sup>18,19</sup>, which drives muscle protein synthesis downstream of Akt<sup>16</sup>. In mammalian tissue, FOXO proteins reduce mTORC1 activity, thereby activating Akt<sup>20</sup>. FOXO proteins therefore may play an intricate role in balancing Akt and mTORC1 activities in response to changing metabolic conditions.

In mouse<sup>21–23</sup> and human<sup>24</sup> skeletal muscle, FOXO3 mRNA or total protein expression or both are upregulated under artificially induced catabolic conditions such as limb suspension or calorie restriction, suggesting that FOXO3 contributes to muscle wasting in these models. Recent rodent studies using immobilization models point toward myofiber type-specific regulation of FOXO3<sup>23,25</sup>. However, a recent study showed no difference in *FOXO3* mRNA levels or in the cytoplasmic levels of the inactive phosphorylated FOXO3 protein in overweight young men subjected to energy restriction<sup>26</sup>, potentially because other factors pertaining to insulin signaling may be at play. The complexity of FOXO protein regulation and the redundancy of FOXO alleles suggest that changes in gene and protein expression levels need to be interpreted with care, as they may not provide direct insights into the mechanistic processes at play.

Disease-induced catabolic states are also characterized by increased FOXO3 expression levels. *Foxo3* mRNA levels were elevated in the late symptomatic stage of two mouse models of spinal muscular atrophy<sup>27</sup>. FOXO3 was also identified in a network-based analysis comparing serum proteomics in patients with Duchenne muscular dystrophy and age-matched controls<sup>28</sup>, suggesting potential for FOXO3 as a protein biomarker to monitor disease progression in conditions with severe skeletal muscle atrophy. Patients with chronic obstructive pulmonary disease displayed an increased ratio of phosphorylated FOXO3 to total FOXO3 in their muscle when compared with healthy controls with or without sarcopenia<sup>29</sup>.

Whereas higher levels of FOXO3 are typically observed in pathological catabolic conditions, FOXO3 expression patterns are not upregulated in healthy old muscle. Sarcopenic mice display no change in nuclear or total FOXO3 protein expression despite reduced phosphorylation levels that might be indicative of higher FOXO3 activity<sup>30</sup>. We and others showed that *FOXO3* mRNA<sup>31,32</sup> and FOXO3 nuclear protein levels decreased in old human skeletal muscle<sup>33</sup> whereas total or phosphorylated FOXO3 protein expression did not change<sup>34</sup>. It is generally accepted that sarcopenia cannot be attributed to an upregulation of the proteolytic system or an induction of FOXO3<sup>35</sup>. Therefore, in aging muscle, FOXO3 may be similarly or even less active than in younger muscle or in models of artificially or disease-induced atrophy. Overall, these results confirm the idea that a series of upstream regulatory factors that inhibit FOXO3 transcriptional activity, including peroxisome proliferator-activated receptor gamma coactivator-1-alpha (PGC-1α) and PI3K/Akt itself<sup>20</sup>, protect the muscle from aging-related atrophy<sup>36,37</sup>. In addition, the role of FOXO3 in the process of muscle aging might rely on a fine balance between the regulation of protein turnover<sup>20</sup> and other, protective anti-aging processes, such as the maintenance of the pool of skeletal muscle stem cells<sup>38</sup>, which is discussed below.

## FOXO3 and the genetics of longevity

*FOXO3* is among the few genes associated with human longevity that have been consistently replicated. Genetic variants of *FoxO3* are associated with exceptional longevity in worms, flies, and mammals<sup>39</sup>. In humans, *FOXO3* hosts about 40 common, non-coding single-nucleotide polymorphisms

(SNPs) that have been consistently associated with longevity in Caucasian<sup>40–44</sup> and Asian<sup>43,45,46</sup> populations. FOXO3 gene and protein expression is associated with age-related phenotypes in multiple tissues<sup>47</sup>. For example, an age-dependent decrease in FOXO3 protein contributes to the loss of anti-inflammatory behavior in macrophages of old mice<sup>48</sup>. Additionally, FOXO3-deficient mice demonstrate signs of pronounced neural activation, apoptosis, and enteric neuronal loss, indicative of premature aging of the enteric nervous system<sup>48</sup>. FOXO3 overexpression also facilitates autophagy, a process of degradation and recycling of cytoplasmic proteins and organelles that is essential for healthy aging in multiple tissues, including skeletal muscle<sup>49</sup>. However, the key role of FOXO3 in aging seems to be via the maintenance of stem cell homeostasis<sup>50</sup>, including in the brain<sup>51</sup>, blood<sup>52</sup>, and skeletal muscle<sup>38</sup>. Whether the modulation of molecular pathways involved in the age-dependent deterioration of stem cell function can reverse aging phenotypes remains controversial<sup>53</sup>. In skeletal muscle stem cells, termed “satellite cells”, FOXO3 enhances stem cell self-renewal via the activation of Notch signaling, maintaining an available pool of satellite cells that have divided but retain their undifferentiated state<sup>38</sup>. In fact, FOXO proteins play a dual role, and in situations of cellular damage, they can induce cell cycle arrest and senescence while independently repressing stemness signaling<sup>54</sup>. Yet, in humans, despite consistent associations between FOXO3 genetic variants and exceptional longevity<sup>40–46</sup>, a possible link between FOXO3 and healthy aging remains unclear. For example, the G allele of a longevity variant of FOXO3 was associated with a 10% reduction in all-cause mortality in a prospective cohort study of 3,584 older American men<sup>55</sup>. Moreover, in a cross-sectional study including more than 30,000 individuals, the G allele of another longevity variant of FOXO3 was associated with a decrease in concentration of circulating insulin-like growth factor-1 (IGF-1), a marker of insulin resistance and chronic disease<sup>56</sup>. Smaller-scale studies have yielded mixed results, albeit showing consistent trends. In the seminal study on FOXO3 and longevity (n = 615), carriers of FOXO3 longevity variants had lower prevalence of coronary heart disease and insulin resistance<sup>43</sup>, echoing similar findings on hypertension in Japanese-American women<sup>57</sup>. In two recent studies on older Swedes (n = 1,520)<sup>58</sup> and Danes (n = 1,088)<sup>59</sup>, carriers of the longevity alleles had better self-rated health even after accounting for cardiovascular disease incidence<sup>58</sup>, higher activity of daily living, and fewer bone fractures<sup>59</sup>. However, these latter findings did not survive adjustment for multiple testing<sup>59</sup>. Similarly, two functional longevity variants of FOXO3 failed to associate with mortality and age-related phenotypes in another sample of 643 long-lived Danes<sup>60</sup>. A recent whole-genome sequencing study also found no differences in genotype distribution at FOXO3 longevity variants between 511 healthy elderly and 686 controls<sup>61</sup>. However, these small sample sizes suggest that these negative findings may partly reflect a lack of statistical power.

Two recent studies provide insight into how the longevity variants of FOXO3 may act at the molecular and cellular levels. In carriers of the G allele of a longevity variant of FOXO3, the FOXO3 gene was physically closer to its neighboring genes, and when exposed to stress, FOXO3 mRNA expression in lymphoblastoid cell lines derived from carriers increased more than in

cell lines derived from non-carriers<sup>62</sup>. In line with those findings, another study showed that the same genetic variant has enhancer functions and that the G allele allows the creation of a novel transcription factor binding site, which induces FOXO3 mRNA expression in response to diverse stress stimuli<sup>63</sup>.

Collectively, these results suggest that FOXO3 genetic variants contribute to reaching old age, but there is a paucity of human studies that are sufficiently powered to demonstrate the role of FOXO3 in healthy aging<sup>60</sup>. One mechanism of action of the FOXO3 SNPs was only recently uncovered and involves a complex “interactome” whereby cellular stress causes FOXO3 to move close and physically interacts with no fewer than 46 flanking genes on chromosome 6<sup>64</sup>. Rather than just FOXO3, the strong association of FOXO3 with longevity might rely on the central position of FOXO3 in a chromatin domain containing essential genes involved in cell resilience, including autophagy, stress response, energy/nutrient sensing, cell proliferation, apoptosis, and stem cell maintenance<sup>62–64</sup>.

### MicroRNA-mediated regulation of FoxO3

MiRNAs are regulatory, small non-coding RNAs. The physiological effect of most miRNAs is based on the post-transcriptional regulation of mRNA expression or the inhibition of protein translation<sup>65</sup>. Whereas correlations are often made between the expression levels of a specific miRNA and its predicted gene and protein targets, miRNA/mRNA direct regulatory relationships can be confirmed only via the means of luciferase reporter experiments *in vitro*. All of the miRNA/FOXO3 regulatory relationships discussed below were confirmed by luciferase validation.

### MicroRNA regulation in autophagy and apoptosis

Increasing exogenous levels of miR-182 decreased FOXO3 mRNA and protein expression in C<sub>2</sub>C<sub>12</sub> myotubes<sup>66</sup> and FOXO3 protein levels in hair cells<sup>67</sup>. Downstream responses included an attenuation of the mRNA levels of FOXO3 catabolic targets *Fbxo32*, autophagy-related protein 12 (*Atg12*), Cathepsin L (*Ctsl*), and microtubule-associated protein light chain 3 (*Lc3*) following atrophy-inducing dexamethasone treatment in C<sub>2</sub>C<sub>12</sub> myotubes<sup>66</sup> as well as an attenuation of cisplatin-induced apoptosis and increase in cell survival in hair cells<sup>67</sup>. Similar to miR-182, elevated levels of miR-34a reduced FOXO3 protein levels and attenuated lipopolysaccharide-induced autophagic activity in alveolar epithelial type II (AT-II) cells<sup>68</sup>. The opposite effects were observed when miR-34a levels were reduced. Other miRNA targets mediating apoptosis via FOXO3 include miR-223 and miR-155<sup>69–71</sup>. Apoptosis of peripheral blood macrophages is decreased in patients with tuberculosis, while isolated human macrophages transfected with mycobacterium tuberculosis (Mtb) strain H37Rv displayed an increase in endogenous miR-223 levels. These results suggest an association between elevated levels of miR-223 and reduced apoptosis. In support of this, the overexpression of miR-223 in isolated human macrophages reduced apoptosis and suppressed FOXO3 protein levels. The miR-223 inhibitory effect on apoptosis was counteracted by FOXO3 overexpression<sup>71</sup>. Finally, expression levels of miR-155 are increased in renal tissues of rats that have undergone ischemia/reperfusion injury as well as in hypoxia/reoxygenation injury-induced human kidney proximal tubules epithelial (HK2) cells<sup>70</sup>.

Overexpressing miR-155 in HK2 cells repressed FOXO3 mRNA and protein levels, increased caspase-1, interleukin-1 beta (IL-1 $\beta$ ), and IL-18 mRNA and protein levels, and increased pyroptosis, a response that was attenuated by the suppression of miR-155<sup>70</sup>.

### MicroRNA regulation in cell proliferation and growth

Prostate cancer (PC) tissue and primary prostate epithelial cell lines (PC cells) display increased expression levels of endogenous miR-592<sup>72</sup> and miR-1307<sup>73</sup>. Overexpression of these two miRNAs in PC cells inhibited FOXO3 protein levels and increased cell proliferation whereas suppressing their expression reversed these effects. Similarly, miR-592 levels were elevated, and FOXO3 mRNA and protein reduced, in colorectal cancer (CRC) tissues and cells<sup>74</sup>. In contrast, lentiviral-induced inhibition of miR-592 attenuated CRC cell proliferation and clonogenicity<sup>74</sup>. Overexpressing miR-551b, an miRNA that has elevated levels in ovarian cancer tissue, in isolated primary ovarian cancer (OVCA) cells increased proliferation, invasion, and chemoresistance of OVCA stem cells via the suppression of FOXO3 and TRIM31 proteins<sup>75</sup>. *In vivo*, miR-551b inhibition increased the susceptibility of OVCA cells to the chemotherapy drug cisplatin and prolonged the survival of host mice<sup>75</sup>. In contrast, miR-498 levels were decreased in ovarian cancer tissue. Overexpressing miR-498 attenuated OVCA cell proliferation and was associated with a decrease in *Cyclin D1* and increase in *p27* expression, indicating that more cells remained in the G<sub>0</sub>/G<sub>1</sub> phases of the cell cycle<sup>76</sup>. Of particular interest was the observation that the binding of miR-498 to FOXO3 3'-untranslated region increased its expression levels, an effect that is rare but not without precedent<sup>77,78</sup>. Finally, overexpression of miR-142-5p in chicken primary myoblasts<sup>79</sup> and miR-155-5p in human foreskin fibroblasts<sup>80</sup> increased cell proliferation. This effect was mediated via a decrease in FOXO3 in both cell types. In the myoblasts, overexpressing miR-142-5p was associated with an increase in genes known to regulate growth such as *IGF1R*, *IGF2R*, *IGF2BP2*, *MTH10*, and *PGK1*. In the fibroblasts, overexpressing miR-155-5p inhibited cyclin-dependent kinase inhibitor 1B (CDKN1B). These effects were reversed by the inhibition of endogenous levels of these two miRNAs.

This series of recent studies confirms that numerous miRNAs regulate FOXO3, often in a tissue-, cell-, or disease-specific manner. However, to date, the direct miRNA/FOXO3 relationships have been assessed only under non-physiological and *in vitro* conditions. Although this fundamental work is essential and has significantly increased our understanding of the post-transcriptional regulation of FOXO3, research should now shift

toward the *in vivo* regulation of FOXO3 targeting miRNAs in suitable animal models of human disease. Understanding how miRNAs regulate FOXO3 activity is of interest for many fields of biomedical research, as miRNAs potentially constitute novel and effective targets for human therapy<sup>81</sup>.

### Mechanism protecting FOXO3 from microRNA regulation

Two mechanisms have been identified that protect FOXO3 from being targeted by certain miRNAs. The Foxo3 pseudogene (Foxo3P) and the Foxo3 circular RNA (circ-Foxo3) act as a “sponge” to bind miRNAs that normally would target FOXO3. Several miRNAs, including miR-22, miR-136, miR-138, miR-149, miR-433, miR-762, miR-3614-5p, and miR3622b-5p, all interact with FOXO3<sup>82</sup> but do not cause transcript degradation. Competition assays and luciferase reporter assays revealed that Foxo3P and circ-Foxo3 can compete with Foxo3 for binding to these miRNAs. This competitive inhibition results in an increase in FOXO3 translation. Foxo3P and circ-Foxo3 are endogenously expressed in non-cancerous lines such as BEAS2B, HaCaT, and MCF-10A. When these cells are transfected with Foxo3, Foxo3P, or circ-Foxo3 and exposed to hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), cell survival decreases. Additionally, nude mice injected with MDA-MB-231 cells overexpressing Foxo3, Foxo3P, or circ-Foxo3 have small tumor growth, demonstrating that Foxo3P or circ-Foxo3 has functional consequences similar to those of Foxo3.

### Conclusions

FOXO3 has versatile functions in human health and disease, and recent research offers new insights into the molecular mechanisms underlying the role and regulation of this essential transcription factor. Over the last 3 years, an important part of FOXO3 research has focused on longevity studies combining population epidemiology and molecular investigations, and the aim has been to pinpoint the mechanisms that underlie the role of FOXO3 in longevity. Simultaneously, numerous new findings highlight the important role of miRNAs in the regulation of FOXO3 and their implication in the regulation of cell cycle-related processes. Overall, despite a strong association of FOXO3 with aging phenotypes, its role in healthy aging remains unclear, especially in skeletal muscle. This may constitute an exciting focus for research in the future.

### Grant information

The author(s) declared that no grants were involved in supporting this work.

### References

1. Hannehalli S, Kaestner KH: **The evolution of Fox genes and their role in development and disease.** *Nat Rev Genet.* 2009; **10**(4): 233–40.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
2. Clark KL, Halay ED, Lai E, *et al.*: **Co-crystal structure of the HNF-3/fork head DNA-recognition motif resembles histone H5.** *Nature.* 1993; **364**(6436): 412–20.  
[PubMed Abstract](#) | [Publisher Full Text](#)





3. Lai E, Prezioso VR, Smith E, *et al.*: **HNF-3A, a hepatocyte-enriched transcription factor of novel structure is regulated transcriptionally.** *Genes Dev.* 1990; 4(8): 1427–36.  
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Weigel D, Jäckle H: **The fork head domain: a novel DNA binding motif of eukaryotic transcription factors?** *Cell.* 1990; 63(3): 455–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
5. **F** Link W, Fernandez-Marcos PJ: **FOXO transcription factors at the interface of metabolism and cancer.** *Int J Cancer.* 2017; 141(12): 2379–91.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
6. **F** Menon V, Ghaffari S: **Transcription factors FOXO in the regulation of homeostatic hematopoiesis.** *Curr Opin Hematol.* 2018; 25(4): 290–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
7. Webb AE, Brunet A: **FOXO transcription factors: key regulators of cellular quality control.** *Trends Biochem Sci.* 2014; 39(4): 159–69.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
8. **F** Ma J, Matkar S, He X, *et al.*: **FOXO family in regulating cancer and metabolism.** *Semin Cancer Biol.* 2018; 50: 32–41.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
9. **F** Urbánek P, Klotz LO: **Posttranscriptional regulation of FOXO expression: microRNAs and beyond.** *Br J Pharmacol.* 2017; 174(12): 1514–32.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
10. **F** Manning BD, Toker A: **AKT/PKB Signaling: Navigating the Network.** *Cell.* 2017; 169(3): 381–405.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
11. Brunet A, Bonni A, Zigmond MJ, *et al.*: **Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor.** *Cell.* 1999; 96(6): 857–68.  
[PubMed Abstract](#) | [Publisher Full Text](#)
12. Obsilova V, Vecer J, Herman P, *et al.*: **14-3-3 Protein interacts with nuclear localization sequence of forkhead transcription factor FoxO4.** *Biochemistry.* 2005; 44(34): 11608–17.  
[PubMed Abstract](#) | [Publisher Full Text](#)
13. Kops GJ, de Ruiter ND, De Vries-Smits AM, *et al.*: **Direct control of the Forkhead transcription factor AFX by protein kinase B.** *Nature.* 1999; 398(6728): 630–4.  
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Ogg S, Paradis S, Gottlieb S, *et al.*: **The Fork head transcription factor DAF-16 transduces insulin-like metabolic and longevity signals in *C. elegans*.** *Nature.* 1997; 389(6654): 994–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Furuyama T, Nakazawa T, Nakano I, *et al.*: **Identification of the differential distribution patterns of mRNAs and consensus binding sequences for mouse DAF-16 homologues.** *Biochem J.* 2000; 349(Pt 2): 629–34.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
16. Goodman CA: **The role of mTORC1 in regulating protein synthesis and skeletal muscle mass in response to various mechanical stimuli.** *Rev Physiol Biochem Pharmacol.* 2014; 166: 43–95.  
[PubMed Abstract](#) | [Publisher Full Text](#)
17. **F** Sandri M, Sandri C, Gilbert A, *et al.*: **Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy.** *Cell.* 2004; 117(3): 399–412.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
18. **F** Jia K, Chen D, Riddle DL: **The TOR pathway interacts with the insulin signaling pathway to regulate *C. elegans* larval development, metabolism and life span.** *Development.* 2004; 131(16): 3897–906.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
19. **F** Puig O, Marr MT, Ruhf ML, *et al.*: **Control of cell number by *Drosophila* FOXO: downstream and feedback regulation of the insulin receptor pathway.** *Genes Dev.* 2003; 17(16): 2006–20.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
20. Chen CC, Jeon SM, Bhaskar PT, *et al.*: **FoxOs inhibit mTORC1 and activate Akt by inducing the expression of Sestrin3 and Rictor.** *Dev Cell.* 2010; 18(4): 592–604.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
21. Furuyama T, Kitayama K, Yamashita H, *et al.*: **Forkhead transcription factor FOXO1 (FKHR)-dependent induction of PDK4 gene expression in skeletal muscle during energy deprivation.** *Biochem J.* 2003; 375(Pt 2): 365–71.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
22. Kamei Y, Mizukami J, Miura S, *et al.*: **A forkhead transcription factor FKHR up-regulates lipoprotein lipase expression in skeletal muscle.** *FEBS Lett.* 2003; 536(1–3): 232–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
23. **F** Okamoto T, Machida S: **Changes in FOXO and proinflammatory cytokines in the late stage of immobilized fast and slow muscle atrophy.** *Biomed Res.* 2017; 38(6): 331–42.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
24. Mercken EM, Crosby SD, Lamming DW, *et al.*: **Calorie restriction in humans inhibits the PI3K/AKT pathway and induces a younger transcription profile.** *Aging Cell.* 2013; 12(4): 645–51.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
25. **F** Brocca L, Toniolo L, Reggiani C, *et al.*: **FoxO-dependent atrogenes vary among catabolic conditions and play a key role in muscle atrophy induced by hindlimb suspension.** *J Physiol.* 2017; 595(4): 1143–58.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
26. **F** Hector AJ, McGlory C, Damas F, *et al.*: **Pronounced energy restriction with elevated protein intake results in no change in proteolysis and reductions in skeletal muscle protein synthesis that are mitigated by resistance exercise.** *FASEB J.* 2018; 32(1): 265–75.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
27. **F** Deguise MO, Boyer JG, McFall ER, *et al.*: **Differential induction of muscle atrophy pathways in two mouse models of spinal muscular atrophy.** *Sci Rep.* 2016; 6: 28846.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
28. **F** Parolo S, Marchetti L, Lauria M, *et al.*: **Combined use of protein biomarkers and network analysis unveils deregulated regulatory circuits in Duchenne muscular dystrophy.** *PLoS One.* 2018; 13(3): e0194225.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
29. **F** Kneppers AEM, Langen RCJ, Gosker HR, *et al.*: **Increased Myogenic and Protein Turnover Signaling in Skeletal Muscle of Chronic Obstructive Pulmonary Disease Patients With Sarcopenia.** *J Am Med Dir Assoc.* 2017; 18(7): 637.e1–637.e11.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
30. **F** Wagatsuma A, Shiozuka M, Takayama Y, *et al.*: **Effects of ageing on expression of the muscle-specific E3 ubiquitin ligases and Akt-dependent regulation of Foxo transcription factors in skeletal muscle.** *Mol Cell Biochem.* 2016; 412(1–2): 59–72.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
31. Drummond MJ, Addison O, Brunker L, *et al.*: **Downregulation of E3 ubiquitin ligases and mitophagy-related genes in skeletal muscle of physically inactive, frail older women: a cross-sectional comparison.** *J Gerontol A Biol Sci Med Sci.* 2014; 69(8): 1040–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
32. **F** Mikkelsen UR, Agergaard J, Couppé C, *et al.*: **Skeletal muscle morphology and regulatory signalling in endurance-trained and sedentary individuals: The influence of ageing.** *Exp Gerontol.* 2017; 93: 54–67.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
33. Léger B, Derave W, De Bock K, *et al.*: **Human sarcopenia reveals an increase in SOCS-3 and myostatin and a reduced efficiency of Akt phosphorylation.** *Rejuvenation Res.* 2008; 11(1): 163–175B.  
[PubMed Abstract](#) | [Publisher Full Text](#)
34. Stefanetti RJ, Zacharewicz E, Della Gatta P, *et al.*: **Ageing has no effect on the regulation of the ubiquitin proteasome-related genes and proteins following resistance exercise.** *Front Physiol.* 2014; 5: 30.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
35. Sandri M, Barberi L, Bijaś AY, *et al.*: **Signalling pathways regulating muscle mass in ageing skeletal muscle: the role of the IGF1-Akt-mTOR-FoxO pathway.** *BioGerontology.* 2013; 14(3): 303–23.  
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Sandri M, Lin J, Handschin C, *et al.*: **PGC-1alpha protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription.** *Proc Natl Acad Sci U S A.* 2006; 103(44): 16260–5.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
37. **F** Stitt TN, Drujan D, Clarke BA, *et al.*: **The IGF-1/PI3K/Akt pathway prevents expression of muscle atrophy-induced ubiquitin ligases by inhibiting FOXO transcription factors.** *Mol Cell.* 2004; 14(3): 395–403.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
38. Gopinath SD, Webb AE, Brunet A, *et al.*: **FOXO3 promotes quiescence in adult muscle stem cells during the process of self-renewal.** *Stem Cell Reports.* 2014; 2(4): 414–26.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
39. Kenyon CJ: **The genetics of ageing.** *Nature.* 2010; 464(7288): 504–12.  
[PubMed Abstract](#) | [Publisher Full Text](#)
40. Anselmi CV, Malovini A, Roncarati R, *et al.*: **Association of the FOXO3A locus with extreme longevity in a southern Italian centenarian study.** *Rejuvenation Res.* 2009; 12(2): 95–104.  
[PubMed Abstract](#) | [Publisher Full Text](#)
41. **F** Flachsbarb F, Caliebe A, Kleindorff R, *et al.*: **Association of FOXO3A variation with human longevity confirmed in German centenarians.** *Proc Natl Acad Sci U S A.* 2009; 106(8): 2700–5.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
42. Soerensen M, Dato S, Christensen K, *et al.*: **Replication of an association of variation in the FOXO3A gene with human longevity using both case-control and longitudinal data.** *Aging Cell.* 2010; 9(6): 1010–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. Willcox BJ, Donlon TA, He Q, *et al.*: **FOXO3A genotype is strongly associated with human longevity.** *Proc Natl Acad Sci U S A.* 2008; 105(37): 13987–92.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
44. **F** Pawlikowska L, Hu D, Huntsman S, *et al.*: **Association of common genetic variation in the insulin/IGF1 signaling pathway with human longevity.** *Aging Cell.* 2009; 8(4): 460–72.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
45. Li Y, Wang WJ, Cao H, *et al.*: **Genetic association of FOXO1A and FOXO3A with longevity trait in Han Chinese populations.** *Hum Mol Genet.* 2009; 18(24):

- 4897–904.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
46. Sun L, Hu C, Zheng C, *et al.*: **FOXO3 variants are beneficial for longevity in Southern Chinese living in the Red River Basin: A case-control study and meta-analysis.** *Sci Rep.* 2015; 5: 9852.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  47. **F** Martins R, Lithgow GJ, Link W: **Long live FOXO: unraveling the role of FOXO proteins in aging and longevity.** *Aging Cell.* 2016; 15(2): 196–207.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  48. **F** Becker L, Nguyen L, Gill J, *et al.*: **Age-dependent shift in macrophage polarisation causes inflammation-mediated degeneration of enteric nervous system.** *Gut.* 2018; 67(5): 827–36.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  49. **F** ENCODE Project Consortium, Birney E, Stamatoyannopoulos JA, *et al.*: **Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project.** *Nature.* 2007; 447(7146): 799–816.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  50. Liang R, Ghaffari S: **Stem Cells Seen Through the FOXO Lens: An Evolving Paradigm.** *Curr Top Dev Biol.* 2018; 127: 23–47.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  51. Santo EE, Paik J: **FOXO in Neural Cells and Diseases of the Nervous System.** *Curr Top Dev Biol.* 2018; 127: 105–18.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  52. **F** Bigarella CL, Li J, Rimmelé P, *et al.*: **FOXO3 Transcription Factor Is Essential for Protecting Hematopoietic Stem and Progenitor Cells from Oxidative DNA Damage.** *J Biol Chem.* 2017; 292(7): 3005–15.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  53. Oh J, Lee YD, Wagers AJ: **Stem cell aging: mechanisms, regulators and therapeutic opportunities.** *Nat Med.* 2014; 20(8): 870–80.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  54. de Keizer PL: **The Fountain of Youth by Targeting Senescent Cells?** *Trends Mol Med.* 2017; 23(1): 6–17.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  55. **F** Willcox BJ, Tranah GJ, Chen R, *et al.*: **The FoxO3 gene and cause-specific mortality.** *Aging Cell.* 2016; 15(4): 617–24.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  56. **F** Teumer A, Qi Q, Nethander M, *et al.*: **Genomewide meta-analysis identifies loci associated with IGF-I and IGFBP-3 levels with impact on age-related traits.** *Aging Cell.* 2016; 15(5): 811–24.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  57. Morris BJ, Chen R, Donlon TA, *et al.*: **Association Analysis of FOXO3 Longevity Variants With Blood Pressure and Essential Hypertension.** *Am J Hypertens.* 2016; 29(11): 1292–300.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  58. **F** Zettergren A, Kern S, Rydén L, *et al.*: **Genetic variation in FOXO3 is associated with self-rated health in a population-based sample of older individuals.** *J Gerontol A Biol Sci Med Sci.* 2018.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  59. Soerensen M, Nygaard M, Dato S, *et al.*: **Association study of FOXO3A SNPs and aging phenotypes in Danish oldest-old individuals.** *Aging Cell.* 2015; 14(1): 60–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  60. **F** Flachsbart F, Dose J, Gentschew L, *et al.*: **Identification and characterization of two functional variants in the human longevity gene FOXO3.** *Nat Commun.* 2017; 8(1): 2063.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  61. Erikson GA, Bodian DL, Rueda M, *et al.*: **Whole-Genome Sequencing of a Healthy Aging Cohort.** *Cell.* 2016; 165(4): 1002–11.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  62. **F** Donlon TA, Willcox BJ, Morris BJ: **FOXO3 cell resilience gene neighborhood.** *Aging (Albany NY).* 2017; 9(12): 2467–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  63. **F** Grossi V, Forte G, Sanese P, *et al.*: **The longevity SNP rs2802292 uncovered: HSF1 activates stress-dependent expression of FOXO3 through an intronic enhancer.** *Nucleic Acids Res.* 2018; 46(11): 5587–600.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  64. **F** Donlon TA, Morris BJ, Chen R, *et al.*: **FOXO3 longevity interactome on chromosome 6.** *Aging Cell.* 2017; 16(5): 1016–25.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  65. Bartel DP: **MicroRNAs: genomics, biogenesis, mechanism, and function.** *Cell.* 2004; 116(2): 281–97.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  66. Hudson MB, Rahner JA, Zheng B, *et al.*: **miR-182 attenuates atrophy-related gene expression by targeting FoxO3 in skeletal muscle.** *Am J Physiol Cell Physiol.* 2014; 307(4): C314–9.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  67. **F** Li Y, Li A, Wu J, *et al.*: **miR-182-5p protects inner ear hair cells from cisplatin-induced apoptosis by inhibiting FOXO3a.** *Cell Death Dis.* 2016; 7(9): e2362.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  68. **F** Song L, Zhou F, Cheng L, *et al.*: **MicroRNA-34a Suppresses Autophagy in Alveolar Type II Epithelial Cells in Acute Lung Injury by Inhibiting FoxO3 Expression.** *Inflammation.* 2017; 40(3): 927–36.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  69. Lou K, Chen N, Li Z, *et al.*: **MicroRNA-142-5p Overexpression Inhibits Cell Growth and Induces Apoptosis by Regulating FOXO in Hepatocellular Carcinoma Cells.** *Oncol Res.* 2017; 25(1): 65–73.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  70. **F** Wu H, Huang T, Ying L, *et al.*: **miR-155 is Involved in Renal Ischemia-Reperfusion Injury via Direct Targeting of FoxO3a and Regulating Renal Tubular Cell Pyroptosis.** *Cell Physiol Biochem.* 2016; 40(6): 1692–705.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  71. Xi X, Zhang C, Han W, *et al.*: **MicroRNA-223 Is Upregulated in Active Tuberculosis Patients and Inhibits Apoptosis of Macrophages by Targeting FOXO3.** *Genet Test Mol Biomarkers.* 2015; 19(12): 650–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  72. Lv Z, Rao P, Li W: **miR-592 represses FOXO3 expression and promotes the proliferation of prostate cancer cells.** *Int J Clin Exp Med.* 2015; 8(9): 15246–53.  
[PubMed Abstract](#) | [Free Full Text](#)
  73. **F** Qiu X, Dou Y: **miR-1307 promotes the proliferation of prostate cancer by targeting FOXO3A.** *Biomed Pharmacother.* 2017; 88: 430–5.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  74. **F** Fu Q, Du Y, Yang C, *et al.*: **An oncogenic role of miR-592 in tumorigenesis of human colorectal cancer by targeting Forkhead Box O3A (FoxO3A).** *Expert Opin Ther Targets.* 2016; 20(7): 771–82.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  75. **F** Wei Z, Liu Y, Wang Y, *et al.*: **Downregulation of Foxo3 and TRIM31 by miR-551b in side population promotes cell proliferation, invasion, and drug resistance of ovarian cancer.** *Med Oncol.* 2016; 33(11): 126.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  76. Liu R, Liu F, Li L, *et al.*: **miR-498 regulated FOXO3 expression and inhibited the proliferation of human ovarian cancer cells.** *Biomed Pharmacother.* 2015; 72: 52–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  77. **F** Vasudevan S, Tong Y, Steitz JA: **Switching from repression to activation: microRNAs can up-regulate translation.** *Science.* 2007; 318(5858): 1931–4.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  78. Zhang X, Zuo X, Yang B, *et al.*: **MicroRNA directly enhances mitochondrial translation during muscle differentiation.** *Cell.* 2014; 158(3): 607–19.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  79. **F** Li Z, Abdalla BA, Zheng M, *et al.*: **Systematic transcriptome-wide analysis of mRNA-miRNA interactions reveals the involvement of miR-142-5p and its target (FOXO3) in skeletal muscle growth in chickens.** *Mol Genet Genomics.* 2018; 293(1): 69–80.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  80. **F** Ren L, Zhao Y, Huo X, *et al.*: **miR-155-5p promotes fibroblast cell proliferation and inhibits FOXO signaling pathway in vulvar lichen sclerosis by targeting FOXO3 and CDKN1B.** *Gene.* 2018; 653: 43–50.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  81. van der Ree MH, van der Meer AJ, van Nuenen AC, *et al.*: **Miraviren dosing in chronic hepatitis C patients results in decreased microRNA-122 levels without affecting other microRNAs in plasma.** *Aliment Pharmacol Ther.* 2016; 43(1): 102–13.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  82. **F** Yang W, Du WW, Li X, *et al.*: **Foxo3 activity promoted by non-coding effects of circular RNA and Foxo3 pseudogene in the inhibition of tumor growth and angiogenesis.** *Oncogene.* 2016; 35(30): 3919–31.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)



# Open Peer Review

Current Referee Status:



## Editorial Note on the Review Process

**F1000 Faculty Reviews** are commissioned from members of the prestigious **F1000 Faculty** and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

## The referees who approved this article are:

### Version 1

- 1 **Boudewijn M. T. Burgering** Department of Molecular Cancer Research, University Medical Center Utrecht, Utrecht, Netherlands  
**Competing Interests:** No competing interests were disclosed.
- 2 **Wolfgang Link** Department of Biomedical Sciences and Medicine (DCBM), the Centre for Biomedical Research (CBMR), and Algarve Biomedical Center (ABC), University of Algarve, Campus de Gambelas, Faro, Portugal  
**Competing Interests:** No competing interests were disclosed.
- 3 **Bradley J. Willcox** John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA  
**Competing Interests:** No competing interests were disclosed.
- 4 **Saghi Ghaffari** Department of Cell, Developmental and Regenerative Biology, Black Family Stem Cell Institute, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA  
**Competing Interests:** No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact [research@f1000.com](mailto:research@f1000.com)

**F1000Research**