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TOPICAL REVIEW

# Vitamin D deficiency accelerates ageing and age-related diseases: a novel hypothesis

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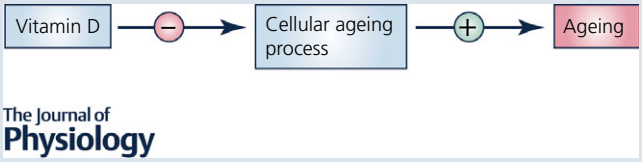


**Abstract** Ageing can occur at different rates, but what controls this variable rate is unknown. Here I have developed a hypothesis that vitamin D may act to control the rate of ageing. The basis of this hypothesis emerged from studyng the various cellular processes that control ageing. These processes such as autophagy, mitochondrial dysfunction, inflammation, oxidative stress, epigenetic changes, DNA disorders and alterations in $Ca^{2+}$ and reactive oxygen species (ROS) signalling are all known to be regulated by vitamin D. The activity of these processes will be enhanced in individuals that are deficient in vitamin D. Not only will this increase the rate of ageing, but it will also increase the probability of developing age-related diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis and cardiovascular disease. In individual with normal vitamin D levels, these ageing-related processes will occur at lower rates resulting in a reduced rate of ageing and enhanced protection against these age-related diseases.

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**Abstract figure legend** The cellular processes that drive the rate of ageing are regulated by Vitamin D.

## Introduction

One of the interesting aspects of ageing is that it can occur at different rates (Grabowska *et al.* 2017). As part of the hypothesis developed here, it is proposed that those individuals that age slowly live a lot longer and have a healthy old age in that they tend not to develop age-related diseases. On the other hand, those that age faster do not survive so long and are likley to develop the age-related diseases such as Alzheimer's disease, Parkinson's disease and cardiovascular disease. Perhaps the best example of how the rate of ageing can vary is the increased ageing that occurs in Hutchinson–Gilford progeria syndrome (HGPS). This premature ageing disorder, which is caused by a mutation in the *LMNA* gene, greatly accelerates the rate of ageing such that young children become old during their teenage years and do not survive much beyond 20 years (Burtner & Kennedy, 2010; Gonzalo *et al.* 2017).

**Michael J. Berridge** is best known for his discovery of inositol trisphosphate ($IP_3$), which plays a universal role in regulating many different cellular processes. He became a Fellow of Trinity College in 1972 and was elected a Fellow of The Royal Society in 1984. For his work on second messengers he has received numerous awards and prizes, including The King Faisal International Prize in Science, The Louis Jeantet Prize in Medicine, The Albert Lasker Medical Research Award, The Heineken Prize, the Shaw Prize, and The Wolf Foundation Prize in Medicine. In 1998 he was knighted for his service to science.



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It is of interest that vitamin D supplementation can slow the increased rate of ageing that occurs during HGPS (Kreienkamp *et al.* 2016).

In order to understand how ageing can occur at different rates, it is necessary to understand what controls the ageing process. There is increasing evidence that ageing is not a single process in that it seems to be driven by a number of cellular processes such as autophagy, mitochondrial dysfunction, inflammation, oxidative stress, epigenetic changes, DNA disorders, and alterations in $Ca^{2+}$ and reactive oxygen species (ROS) signalling (Ding & Shen, 2008; López-Otín *et al.* 2013; Aunan *et al.* 2016; Seals *et al.* 2016; Jylhävä *et al.* 2017). What is remarkable about all of these cellular ageing processes is that their activity is regulated by vitamin D (Fig. 1). This protective function of vitamin D in ageing is markedly enhanced by its ability to control the expression of Nrf2 (Nakai *et al.* 2014) and the anti-ageing protein Klotho (Forster *et al.* 2011), which are also important regulators of multiple cellular signalling systems including the formation of antioxidants. Nrf2 plays a major role in protecting cells against oxidative stress (Lewis *et al.* 2010). Defects in the Klotho gene induces the premature-ageing syndrome in mice (Kuro-o, 2009).

On the basis of this information, I shall develop a hypothesis that this vitamin D–Klotho–Nrf2 signalling network is a key regulator of the rate of ageing. When vitamin D levels are normal, these processes will operate to drive healthy ageing that occurs at a slow rate (Tuohimaa, 2009; Haussler *et al.* 2010). However, when vitamin D is deficient these ageing processes will be enhanced and this will result in an increase in the rate of ageing. An example of how the rate of ageing can vary is the observation that the onset of menopause in women, who have lower levels of vitamin D than men (Looker *et al.* 2011), is enhanced by vitamin D deficiency (Purdue-Smithe *et al.* 2017), i.e., menopause occurs earlier in those women that are deficient in vitamin D. There is also considerable evidence to indicate that vitamin D deficiency is related to mortality (Schöttker *et al.* 2013; Gaksch *et al.* 2017; Ordóñez-Mena *et al.* 2017). A decrease in vitamin D activity has been linked to premature ageing in mice (Keisala *et al.* 2009). In addition, an increase in the activity of these ageing processes during vitamin D deficiency may also set the stage for the onset of many of the age-related disorders such as a decline in cognition, depression, osteoporosis, hypertension and cardiovascular disease, diabetes, cancer, muscle weakness, and Alzheimer's disease (Zittermann, 2003; Annweiler *et al.* 2010; Pittas & Dawson-Hughes, 2010; Meehan & Penckofer, 2014; Banerjee *et al.* 2015; Berridge, 2015*b*, 2016; Costantino *et al.* 2016; Dawson-Hughes, 2017; Wang *et al.* 2017). In the case of cancer, polymorphisms of the vitamin D receptor (VDR) have been linked to the onset of prostate cancer (Liu *et al.* 2017). The fact that the ability of the skin to make vitamin D declines as ageing progresses is one reason why cognition tends to decline during ageing (MacLaughlin & Holick, 1985; Kennel *et al.* 2010; Grady, 2012). In order to develop this hypothesis that the rate of ageing is regulated by vitamin D, I will describe the role of these different ageing processes and how vitamin D carries out its regulatory activity.

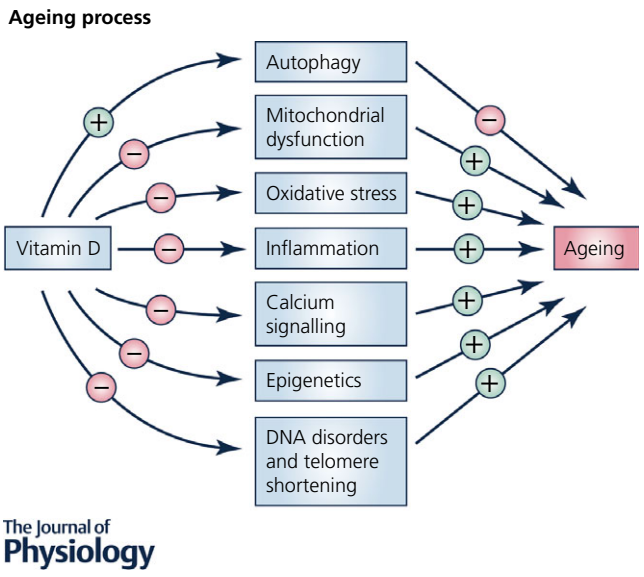


**Figure 1. The vitamin D hypothesis of ageing**
It is proposed that vitamin D acts to regulate ageing by controlling the activity of a number of the ageing processes. Vitamin D promotes the activity of autophagy, which acts to slow down the ageing processes by removing dysfunctional mitochondria. Vitamin D also acts to reduce mitochondrial dysfunction, oxidative stress, inflammation, calcium signalling, epigenetics and DNA disorders including telomere shortening, which act to drive the processes of ageing.

## Autophagy and ageing

There is increasing evidence that autophagy plays a key role in maintaining healthy ageing (Rubinsztein *et al.* 2011; Madeo *et al.* 2015; Plaza-Zabala *et al.* 2017). In those families that have extended longevity, the process of autophagy is better maintained (Raz *et al.* 2017). Autophagy is an essential process in that it maintains healthy cells by removing damaged proteins and malfunctioning organelles, especially the mitochondria (Hubbard *et al.* 2012; Fivenson *et al.* 2017; Palikaras *et al.* 2017). As mitochondria age, there is a decline in their ability to generate ATP and they begin to generate large amounts of reactive oxygen species (ROS). Such an increase in oxidative stress is one of the processes that enhances ageing (Fig. 1; Terman *et al.* 2007; Salminen *et al.* 2012; Ureshino *et al.* 2014). Therefore, to reduce ageing it is essential that these damaged mitochondria are removed by autophagy. It is essential, therefore, that the process of autophagy is

maintained and there is evidence that it may decline when ageing is occurring at a fast rate.

The autophagy process is regulated by changes in the level of $Ca^{2+}$ (Høyer-Hansen *et al.* 2007; Decuypere *et al.* 2011*b*; La Rovere *et al.* 2016; Sun *et al.* 2016; Luyten *et al.* 2017) and by increases in the levels of ROS (Navarro-Yepes *et al.* 2014). The action of $Ca^{2+}$ is complicated because it exerts a dual action on autophagy. For example, an increase in the level of $Ca^{2+}$, especially following the activation of inositol trisphosphate receptors ($InsP_3Rs$), acts to inhibit autophagy (Criollo *et al.* 2007). On the other hand, a reduction in the level of $Ca^{2+}$ also enhances autophagy. It has been proposed that the nature of the cellular state may determine how this dual action of $Ca^{2+}$ occurs (Decuypere *et al.* 2011*b*).

There is now growing evidence that vitamin D plays an important role in maintaining autophagy (Fig. 1; Yuk *et al.* 2009; Høyer-Hansen *et al.* 2010; Verway *et al.* 2010; Wu & Sun, 2011; Jang *et al.* 2014; Uberti *et al.* 2014; Wang *et al.* 2016; Chirumbolo *et al.* 2017; Mushegian, 2017; Tavera-Mendoza *et al.* 2017; Wei *et al.* 2017). It is possible that vitamin D will act to promote autophagy by regulating the level of $Ca^{2+}$ through its ability to promote the expression of $Ca^{2+}$ pumps and $Ca^{2+}$ buffers as will be described in a later section. By maintaining autophagy, vitamin D will reduce the ageing process by ensuring that the mitochondria do not generate excessive amounts of ROS, which have been implicated in ageing as described below.

## Inflammation and ageing

Inflammation has been implicated in the process of ageing (Cevenini *et al.* 2010, 2013; Salminen *et al.* 2012; López-Otín *et al.* 2013; Petersen & Smith, 2016; Di Benedetto *et al.* 2017). Damaged mitochondria may play a role in initiating this increase in inflammation (Green *et al.* 2011). These dysfunctional mitochondria are the result of a decline in autophagy that acts normally to remove such damaged mitochondria as described above (Salminen *et al.* 2012).

One of the important actions of vitamin D is to reduce inflammation (Fig. 1; Garcion *et al.* 1999; Hewison, 2010; Sundar & Rahman, 2011; Briones & Darwish 2012; Berk *et al.* 2013; Alvarez *et al.* 2014; Lucas *et al.* 2014; Wang *et al.* 2014). One way it does this is to reduce the expression of inflammatory cytokines (d'Hellencourt *et al.* 2003; Beilfuss *et al.* 2012; Grossmann *et al.* 2012; Wei & Christakos, 2015), which are such a prominent feature of how inflammatory responses alter cellular activity. One of these inflammatory cytokines is tumour necrosis factor-$\alpha$ (TNF-$\alpha$), which acts to increase the expression of the $InsP_3Rs$ (Park *et al.* 2009) thus inducing an increase in the level of $Ca^{2+}$, which accelerates ageing as described below.

## Mitochondrial dysfunction and ageing

Mitochondrial dysfunction is one of the main drivers of ageing (Lin & Beal 2006; Petrosillo *et al.* 2008; Wang *et al.* 2013; Yin *et al.* 2016). As a result of their dysfunction, the mitochondria produce insufficient ATP but generate increased amounts of ROS that enhance oxidative stress (Terman *et al.* 2006, 2010; Petrosillo *et al.* 2008; Toman & Fiskum, 2011; Marzetti *et al.* 2013; Wang *et al.* 2013), which is one of the main drivers of ageing (Fig. 1). It is likely that this mitochondrial dysfunction is driven by a deficiency in vitamin D.

One of the main functions of vitamin D is to maintain the activity of the mitochondrial respiratory chain (Consiglio *et al.* 2015). Vitamin D also regulates the expression of the uncoupling protein (UCP), which is located on the inner mitochondrial membrane where it acts to control thermogenesis (Abbas, 2016). During vitamin D deficiency, mitochondrial respiration declines due to a reduction in the nuclear mRNA molecules and proteins that contribute to mitochondrial respiration (Kim *et al.* 2014; Scaini *et al.* 2016). In particular, the formation of ATP declines because there is a vitamin D-dependent reduction in the expression of complex I of the electron transport chain. This decline in the electron transport chain also results in an increase in the formation of ROS, which induce oxidative stress, which is a feature of ageing (Brownlee, 2005; Lowell & Shulman, 2005) as described in the following section.

Members of the sirtuin family, such as sirtuin (SIRT) 1, also play an important role in maintaining normal mitochondrial function (Westphal *et al.* 2007). The sirtuins, which are $NAD^+$-dependent protein deacetylases, function as anti-ageing proteins that reduce ageing by regulating a wide range of protein targets (Guarente, 2007; Law *et al.* 2009; Donmez & Guarente, 2010; Grabowska *et al.* 2017). The sirtuins also play an important role in reducing brain ageing (Satoh *et al.* 2017). SIRT1 contributes to mitochondrial biogenesis by activating PGC-1$\alpha$. These beneficial effects of SIRT1 on mitochondrial function are regulated by vitamin D, which acts by increasing the formation of SIRT1 (An *et al.* 2010; Polidoro *et al.* 2013; Chang & Kim, 2016; Marampon *et al.* 2016; Manna *et al.* 2017).

One of the main actions of vitamin D is to maintain the normal mitochondrial control of cellular bioenergetics (Calton *et al.* 2015). The $Ca^{2+}$ buffering role of dysfunctional mitochondria is also compromised resulting in an increase in the intracellular level of $Ca^{2+}$, which is a feature of ageing as described later.

## Oxidative stress and ageing

Oxidative stress, which is one of the main drivers of ageing (Finkel & Holbrook, 2000; Stadtman, 2002; Brewer, 2010;

Paradies *et al.* 2011; Ureshino *et al.* 2014; Petersen & Smith, 2016), is caused by the increase in ROS formation by dysregulated mitochondria as described above. Vitamin D plays a major role in regulating ROS levels through its ability to control the expression of cellular antioxidants as part of its role to maintain phenotypic stability of cell signalling pathways (Dong *et al.* 2012; George *et al.* 2012; Berridge, 2015*a*,b). Vitamin D also supports such redox control by maintaining normal mitochondrial function (Bouillon & Verstuyf, 2013; Ryan *et al.* 2016) as described earlier.

Many of the genes that are controlled by the vitamin D–Klotho–Nrf2 regulatory network function to maintain redox homeostasis. For example, vitamin D together with Klotho and Nrf2 increases cellular antioxidants to maintain the normal reducing environment within the cell thereby preventing oxidative stress by removing ROS. For example, the expression of $\gamma$-glutamyl transpeptidase, glutamate cysteine ligase and glutathione reductase, which contribute to the synthesis of the major redox buffer glutathione (GSH), is regulated by vitamin D. Vitamin D also increases the activity of glucose-6-phosphate dehydrogenase to increase the formation of GSH. It down-regulates the nitrogen oxide (NOX) that generates ROS while upregulating the superoxide dismutase that rapidly converts $O_2^{-\bullet}$ to $H_2O_2$ (Berridge, 2016). Vitamin D also up-regulates expression of the glutathione peroxidase that drives the conversion of $H_2O_2$ to water.

## $Ca^{2+}$ signalling and ageing

An alteration in the $Ca^{2+}$ signalling pathway has also be linked to an acceleration in the process of ageing (Fig. 1; Mattson, 2007; Puzianowska-Kuznicka & Kuznicki 2009; Ureshino *et al.* 2010; Decuypere *et al.* 2011*a*; Gant *et al.* 2014; Berridge, 2016; Veldurthy *et al.* 2016; Martin & Bernard, 2017). During ageing, there is an alteration in $Ca^{2+}$ signalling in atrial myocytes (Herraiz-Martínez *et al.* 2015) and neurons (Buchholz *et al.* 2007; Murchison & Griffith, 2007). The relationship between $Ca^{2+}$ signalling and ageing is particularly evident in the ageing brain (Thibault *et al.* 2001; Foster & Kumar, 2002; Gant *et al.* 2006; Foster, 2007; Thibault *et al.* 2007; Kumar *et al.* 2009; Gant *et al.* 2014). An increase in the release of $Ca^{2+}$ from internal stores by the $InsP_3Rs$ and ryanodine receptors (RYRs) contributes to this increase in neural $Ca^{2+}$ levels during ageing (Banerjee & Hasan, 2005; Puzianowska-Kuznicka & Kuznicki, 2009; Santulli & Marks 2015). The increase in $Ca^{2+}$ release from the RYRs is caused by a decline in the expression of the FK506-binding proteins 1a and 1b (FKBP1a/1b), which act normally to reduce the release of $Ca^{2+}$ by the RYRs (Gant *et al.* 2014). Inserting an adeno-associated viral vector bearing a transgene encoding FKBP1b was able to reduce the effects of the elevated levels of $Ca^{2+}$ that function to impair cognitive functions that occur during ageing (Gant *et al.* 2015).

When considering the role of $Ca^{2+}$ in ageing, it is important to include magnesium, which is closely linked to both vitamin D and $Ca^{2+}$. One the functions of magnesium is to enhance the synthesis of vitamin D (Rude *et al.* 1985; Risco & Traba, 1992; Deng *et al.* 2013). There are now indications that low levels of magnesium are linked to a number of diseases that are also associated with vitamin D deficiency. For example, a deficieny in magnesium has been linked to ageing. Lower magnesium levels have been found in individuals with hypertension and metabolic syndrome (Rotter *et al.* 2015). Low blood pressure and an increased risk of stroke have also been observed in individual with low magnesium levels (Bain *et al.* 2015). Some of the actions of magnesium are mediated through a reduction in $Ca^{2+}$ signalling processes. In the brain, extracacellular magnesium can reduce $Ca^{2+}$ entry through voltage-gated $Ca^{2+}$ channels and NMDA receptors (Wilmott & Thompson 2013). An increase in magnesium in the brain reverses the decline in cognition in Alzheimer's disease (Li *et al.* 2014). It is clear from all this evidence that magnesium plays an important role in regulating the activity of both $Ca^{2+}$ and vitamin D.

During ageing, there is a decline in the level of the $Ca^{2+}$ buffer calbindin-$D_{28K}$ in the cholinergic neurons in the brain (Riascos *et al.* 2011). In motoneurons, vitamin D acts to increase the expression of calbindin-D28 and parvalbumin (Alexianu *et al.* 1998). High levels of these buffers contributes to the low levels of $Ca^{2+}$. A decline in these buffers, caused by a decline in the level of vitamin D that occurs during ageing, will result in an elevation of the level of $Ca^{2+}$, which is a feature of brain ageing. In the ageing brain, there also is a decrease in the expression of Bcl-2 (Ureshino *et al.* 2010), which may contribute to the increase in $Ca^{2+}$ release by the $InsP_3Rs$. Bcl-2 interacts with the $InsP_3Rs$ to reduce the release of $Ca^{2+}$ (Distelhorst & Bootman 2011). One of the consequences of this increase in the levels of $Ca^{2+}$ during brain ageing is a decline in cognition (Thibault *et al.* 2001, 2007; Foster 2007; Toescu & Verkhratsky, 2007; Toepper, 2017). This decline in cognition is particularly evident in ageing patients (Seamans *et al.* 2010). In addition to this decline in cognition, there also is evidence of a decline in sleep in older adults, which may contribute to the decline in cognition (Mander *et al.* 2017).

Vitamin D has been shown to alleviate this enhanced $Ca^{2+}$ elevation in the ageing brain. By reducing the levels of $Ca^{2+}$, vitamin D restores normal cognitive function (Landfield & Cadwallader-Neal, 1998; Brewer *et al.* 2006; Przybelski & Binkley, 2007; Perna *et al.* 2014; Schlögl & Holick, 2014; Toffanello *et al.* 2014; Banerjee *et al.* 2015). Strong support for such a notion has come from the study of the decline in cognition in ageing rats that is driven by a marked increase in the amplitude of the

slow after-hyperpolarization (sAHP) that depends on a build-up of $Ca^{2+}$ that activates the SK potassium channel (Landfield, 1987). This $Ca^{2+}$ signal, which depends on the opening of L-type voltage-dependent $Ca^{2+}$ channels that provides trigger $Ca^{2+}$ to activate RYRs, inhibits memory by curtailing the spiking activity necessary for LTP, whereas the increase in $Ca^{2+}$ stimulates calcineurin to induce the long-term depolarization that erases memories. The development of this sAHP during ageing depends on dysregulation of both $Ca^{2+}$ and ROS signalling that can be directly attributed to vitamin D deficiency.

One of the consequences of the elevation of $Ca^{2+}$ and ROS that occurs during vitamin D deficiency is an increase in the incidence of age-related diseases. For example, the onset of Alzheimer's disease occurs in those individuals who are deficient in vitamin D (Banerjee *et al.* 2015) and thus have abnormally elevated levels of both $Ca^{2+}$ and ROS, which may induce the formation of the pathological amyloid beta ($A\beta$) oligomers that then initiate the onset of Alzheimer's disease (Berridge, 2016). Such a possibility is based on the fact that elevated levels of $Ca^{2+}$ act to stimulate the enzymes that form $A\beta$ (Querfurth & Selkoe, 1994; Green & LaFerla, 2008; Itkin *et al.* 2011). Such an increase in $Ca^{2+}$ that occurs during vitamin D deficiency may also be associated with the onset of other neurodegenerative diseases such as Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis.

Vitamin D acts to increase the expression of both Klotho and Nrf2, which also act to reduce the ageing process. Vitamin D working together with Nrf2 and Klotho plays an essential role in maintaining the phenotypic stability of many cell signalling pathways and particularly the $Ca^{2+}$ and redox signalling systems (Berridge, 2015*a*, b). This vitamin D–Klotho–Nrf2 regulatory system can prevent the dysregulation of $Ca^{2+}$ and ROS signalling through multiple mechanisms. Vitamin D suppress the expression of the L-type $Ca^{2+}$ channel (Brewer *et al.* 2001, 2006) that initiates the $Ca^{2+}$ signal that induces the sAHP and it also maintains the expression of plasma membrane $Ca^{2+}$-ATPase (PMCA) and the $Na^+/Ca^{2+}$ exchanger (NCX1), which extrude $Ca^{2+}$ from the cell. In dendritic cells, vitamin D reduces the level of $Ca^{2+}$ by increasing the expression of the NCX1 that extrudes $Ca^{2+}$ from the cell (Shumilina *et al.* 2010). Klotho, which is an anti-ageing protein (Kim *et al.* 2015), acts to stimulate the $Na^+/K^+$-ATPase responsible for maintaining the $Na^+$ gradient necessary for $Ca^{2+}$ extrusion by NCX1. Finally, premature ageing occurs when Nrf2 is repressed (Kubben *et al.* 2016). Nrf2 increases the expression of many anti-oxidants that ensure that ROS levels are kept low (Lewis *et al.* 2010; Niture *et al.* 2010; Sykiotis *et al.* 2011; Nakai *et al.* 2014), which will prevent the sensitization of the RYRs that are triggering the sAHP and memory erasure.

The central role of vitamin D deficiency in this neuronal dysregulation and cognitive decline can be reversed by treating neurons with vitamin D, which dramatically reduces the sAHP (Brewer *et al.* 2006). When tested on ageing rats, vitamin D was found to enhance hippocampal synaptic function and, more significantly, it could prevent the decline in cognition (Landfield & Cadwallader-Neal, 1998; Latimer *et al.* 2014).

## Epigenetics and ageing

Epigenetic changes in the genome play an important role in the ageing process (Gonzalo, 2010; Gravina & Vijg, 2010; Ford *et al.* 2011; Lillycrop *et al.* 2014; Benayoun *et al.* 2015; Aunan *et al.* 2016; Pal & Tyler, 2016; Sen *et al.* 2016). The main epigenetic change that influences ageing is DNA and histone methylation, which has a marked influence on expression of many of the genes that are responsible for healthy ageing. A good example of this is the fact that such epigenetic changes have been linked to oxidative stress (Hedman *et al.* 2016). As described earlier, such oxidative stress is enhanced by a decline in the expression of cellular antioxidants. Such a view is supported by the fact that the most important signalling pathways that are maintained by vitamin D are the $Ca^{2+}$ and redox signalling pathways (Berridge, 2016).

One of the major regulators of antioxidant expression is vitamin D and there is increasing evidence that vitamin D also controls the epigenetic landscape of its multiple gene promoters (Hossein-nezhad & Holick, 2012; Hossein-nezhad & Holick, 2013; Fetahu *et al.* 2014; Xue *et al.* 2016). Both the acetylation and methylation states of its promotor regions are maintained by vitamin D. With regard to acetylation, the vitamin D receptor (VDR) complex recruits histone acetylases such as p300–CREB-binding protein (CBP) and steroid receptor coactivator 1 (SRC-1). Perhaps its most significant action is to increase the expression of a number of DNA demethylases. Control of demethylation is critical because many of the genes regulated by vitamin D are silenced by methylation of the CpG islands located in their promotor regions. Such hypermethylation can also account for a decline in the expression of Klotho that occurs during ageing (King *et al.* 2011). Such age-dependent hypermethylation is also evident in many age-related diseases (cancer, cardiovascular and neurodegenerative diseases; van Otterdijk *et al.* 2013). For example, hypermethylation of promotors in GABAergic neurons may contribute to the phenotypic remodelling responsible for schizophrenia and bipolar disorder (Guidotti *et al.* 2011). Since many of these diseases have also been linked to vitamin D deficiency, it is not surprising to find that vitamin D can modulate the epigenetic landscape. Vitamin D controls the expression of a number of key DNA demethylases such as Jumonji C domain-containing demethylase (JMJD) 1A, JMJD3,

lysine-specific demethylase (LSD) 1 and LSD2 (Pereira *et al.* 2012), which contributes to its ability to maintain phenotypic stability.

### DNA disorders and ageing

Two DNA disorders contribute to the ageing process: telomere shortening and DNA alterations caused by the defective repair of DNA double-strand breaks (DSB); both cause genomic instability (Ding & Shen, 2008; Gonzalez-Suarez *et al.* 2011; López-Otín *et al.* 2013; Chow & Herrup, 2015; Aunan *et al.* 2016). It is of interest that both these defects can be reduced by vitamin D. Telomeres, which are located at the ends of chromosomes, play an important role in preventing the ends of chromosomes from fusing with neighbouring chromosomes (Campisi *et al.* 2001; Oeseburg *et al.* 2010; Prasad *et al.* 2017). During ageing, there is a decline in the length of these telomeres and this causes a decline in cell proliferation resulting in cell senescence, which characterizes the ageing processes (Prasad *et al.* 2017). There is increasing evidence that vitamin D can act to reduce the rate of telomere shortening (Hoffecker *et al.* 2013; Liu *et al.* 2013; Pusceddu *et al.* 2015; Beilfuss *et al.* 2017; Mazidi *et al.* 2017). SIRT6 can also play an important role in stabilizing both the genome and telomeres (Tennen & Chua, 2011).

The defective repair of DNA double-strand breaks (DSBs) is another DNA disorder that contributes to ageing. A deficiency of p53-binding protein 1 (53BP1), which is a key factor in DNA DSBs, is the cause of the defective DSB. It has been established that the cysteine protease cathepsin L (CTSL) is responsible for degrading 53BP1 (Gonzalez-Suarez *et al.* 2011; Grotsky *et al.* 2013). Vitamin D acts to prevent this DNA disorder caused by DSBs by inhibiting CTSL, which leads to the stabilizatioin of 53BP1 (Gonzalez-Suarez *et al.* 2011; Grotsky *et al.* 2013).

### Conclusion

There is increasing evidence that ageing can proceed at variable rates. In this review, I have developed the hypothesis that vitamin D may play a major role in regulating the rate of ageing. The basis of this hypothesis is that a number of the processes that drive ageing (e.g. autophagy, mitochondrial dysfunction, inflammation, oxidative stress, epigenetics, DNA disorders, and alterations in $Ca^{2+}$ and ROS signalling) are regulated by vitamin D. Normal levels of vitamin D are capable of maintaining these processes at their normal low rates and this slows down the ageing process and also helps to prevent the onset of a number of age-related diseases (e.g. Alzheimer's disease, Parkinson's disease, multiple sclerosis, hypertension and cardiovascular disease).

When vitamin D is deficient, there is an increase in the activity of these ageing processes that not only accelerates the rate of ageing, but it also creates the conditions that initiate the onset of the age-related diseases such as Alzheimer's disease. Such an increase in $Ca^{2+}$ that occurs during vitamin D deficiency has also been associated with the onset of other neurodegenerative diseases such as Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis.

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## Additional information

### Competing interests

There are no competing interests.