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Vitamin D, Vitamin D Receptor, and Macroautophagy in Inflammation and Infection

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Abstract

Vitamin D is involved in mineral and bone homeostasis, immune responses, anti-inflammation, anti-infection, and cancer prevention. Vitamin D receptor (VDR) is a nuclear receptor that mediates most biological functions of $1,25(OH)_2D_3$ or vitamin D_3, the active form of vitamin D. Recently, vitamin D_3-induced autophagy has been reported. Autophagy is a lysosome-mediated catabolic pathway classified into three different types: macroautophagy, microautophagy, and chaperone-mediated autophagy. Autophagy contributes to anti-aging, antimicrobial defense, and tumor suppression. The functions of autophagy overlap remarkably with those of vitamin D/VDR signaling. This review focuses on vitamin D_3, VDR, and macroautophagy in inflammation and infection. We place emphasis on the regulatory roles of vitamin D_3 on autophagy at different steps, including induction, nucleation, elongation to maturation, and degradation. We summarize the known molecular mechanisms of vitamin D/VDR signaling on autophagy homeostasis. The potential application of the insights gleaned from these research findings to anti-inflammation and anti-infection is also discussed.

Introduction

Vitamin D deficiency is a critical factor in the pathology of at least 17 varieties of cancer, as well as autoimmune diseases, diabetes, osteoarthritis, periodontal disease, and more (Adorini and Penna, 2008; Blaney et al., 2009; Campbell et al., 2010; Cannell et al., 2008; Gocek and Studzinski, 2009; Grau et al., 2003; Heaney, 2008) (http://www.vitamindcouncil.org). Vitamin D receptor (VDR) is a nuclear receptor that mediates most biological functions of vitamin D_3, the active form of vitamin D (Baeke et al., 2010). Activation of VDR signaling affects many processes, including calcium metabolism, apoptosis, immunity, and autophagy (Bikle, 2010; Hewison, 2008; Jo, 2010; Norman, 2008; White, 2008). Autophagy influences various aspects of disease progression, including stress adaptation, lifespan extension, development, immunity, and cancer (Brest et al., 2010; Levine and Kroemer, 2008; White et al., 2010; De Meyer et al., 2009). There is increasing concern regarding the use of vitamin D as a cheap and convenient supplement for disease prevention. In this article, we review the recent advances of the signaling pathways associated with vitamin D/VDR and autophagy. We discuss the molecular mechanisms and potential application of vitamin D_3 signaling to autophagy homeostasis.

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Vitamin D and VDR

There are two biologically relevant forms of vitamin D. One is ergocalciferol, or vitamin D_2, and the other is cholecalciferol, or vitamin D_3. The enzyme 25-hydroxyvitamin D-1alpha-hydroxylase, which catalyzes 25-hydroxyvitamin D_3 into $1,25(OH)_2D_3$, is critical to the production of the active form of vitamin D. After being taken up by target cells, vitamin D_3 binds to its cognate receptor, VDR.

VDR is a member of the nuclear receptor superfamily (Adams et al., 2004). In mammals, VDR is highly expressed in metabolic tissues, such as intestine, kidney, skin, and thyroid gland, and moderately expressed in nearly all tissues (Bookout et al., 2006; Norman, 2008). Moreover, VDR is expressed in many malignant tissues (Sertznig et al., 2009; Silvagno et al., 2010). Active VDR binds to vitamin D response elements (VDREs) located in promoter regions of target genes, thereby controlling the transcription of these genes (Carlberg, 2003; Haussler et al., 2008). VDR affects the transcription of at least 913 genes in human SCC25 cells (head and neck squamous cell carcinoma cell line) (Wang et al., 2005). The impacted biological processes range from calcium metabolism to the expression of key antimicrobial peptides (Albert et al., 2009; Kamen and Tangpricha, 2010; Sun, 2010). Therefore, it is not surprising that vitamin D_3/VDR signaling is involved in mineral and bone homeostasis, modulation of growth, cardiovascular processes, cancer prevention, and regulation of immune responses, including autophagy. Dysfunction of VDR and vitamin D_3 deficiency can cause poor bone development and health, as well as increase the risk of many chronic diseases, including type 1 diabetes, rheumatoid arthritis, Crohn's disease, infectious diseases, and cancer (Holick, 2010).

Autophagy

Autophagy is a lysosome-mediated catabolic pathway that occurs ubiquitously in all eukaryotic cells (Reggiori and Klionsky, 2002). Depending on the route of delivery to the lysosome, autophagy is classified into three different types: macroautophagy (delivery of cytosolic contents to the lysosome by autophagosomes), microautophagy (inward invagination of the lysosomal membrane), and chaperone-mediated autophagy (direct translocation across the lysosomal membrane) (Mizushima and Levine, 2010). We focus on macroautophagy, which is hereafter simply termed autophagy, in this review.

The process of mammalian autophagy is divided into six principal steps: initiation or induction, nucleation, elongation, closure, maturation, and degradation or extrusion (Kang et al., 2011). Nucleation is the formation of the isolation membrane/phagophore. The nascent membranes are fused at their edges to form double-membrane vesicles, called autophagosomes. Elongation and closure lead to completion of the mature autophagosome (Vellai, 2009). The autophagosome fuses with a lysosome to form an autolysosome, and then its content is degraded (Levine et al., 2011, 2008; Roy and Debnath, 2010). More than 30 autophagy-related genes (ATG) regulate autophagy at the molecular level (Huang and Klionsky, 2007).

The housekeeping function of autophagy is to maintain cellular energy levels and cell survival by recycling amino acids and fatty acids during periods of metabolic stress (Onodera and Ohsumi, 2005; Levine et al., 2008). Moreover, autophagy protects the cell by degrading damaged proteins and organelles as well as intracellular pathogens. The functions of autophagy include tumor suppression (Roy and Debnath, 2010), antimicrobial defense (Deretic, 2010), inhibition of cardiac hypertrophy (De Meyer and Martinet, 2009), anti-aging (Vellai, 2009), and others (Fleming, 2011). Remarkably, the functions of autophagy overlap with those of the vitamin D/VDR signaling.

Pathways Involved in Vitamin D_3-associated Autophagy

Autophagy can be induced by cellular stress, including starvation, hypoxia, biologic agents, and chemicals. Some studies have reported autophagy induced by vitamin D_3 and its analogs in human myeloid leukemia cells, macrophages, breast cancer cells, and head and neck squamous cancer cells (Table 1) (Demasters et al., 2006; Hoyer-Hansen et al., 2005). The signaling pathways regulated by vitamin D_3 include Bcl-2, beclin-1, mammalian target of rapamycin (mTOR), the class III phosphatidylinositol 3-kinase complex (PI3KC3), cathelicidin, calcium metabolism, and cyclin-dependent kinase (Table 1). These pathways are critical in host defense and inflammatory responses. Hence, vitamin D_3 and autophagy are associated with innate immunity (Fabri and Modlin, 2009; Jo, 2010; Liu and Modlin, 2008), inflammatory bowel diseases (Verway et al., 2010), infection, and cancer (Gewirtz et al., 2009; Hoyer-Hansen et al., 2010).

According to recent reports, vitamin D_3 signaling is able to regulate autophagy at the following steps (Figure 1):

1. Vitamin D_3 increases free cytosolic calcium and decreases mTOR induction in autophagy

Vitamin D_3 is a major regulator of calcium metabolism (Fleet, 2006). Increased circulating vitamin D_3 activates VDR, leading to increased intestinal calcium absorption (Song et al., 2003). In excitable cells such as neurons, calcium is released from the sarcoplasmic or endoplasmic reticulum (ER) to activate calcium-dependent kinases and phosphatases, thereby regulating numerous cellular processes, including autophagy. ER calcium induces autophagy when stimulated by vitamin D_3 (Hoyer-Hansen et al., 2007). This process is inhibited by mTOR, a negative regulator of macroautophagy, and induces massive accumulation of autophagosomes in a beclin-1- and ATG7-dependent manner since they are not fused with lysosomes (Hoyer-Hansen et al., 2007). Vitamin D_3 can down-regulate the expression of mTOR protein, thus inducing autophagy by inhibiting the mTORC1 complex (Loewith et al., 2002; Wang et al., 2008).

The Bcl-2 family also regulates autophagy (Chipuk et al., 2010). The published reports on the relationships between vitamin D_3 and Bcl-2 are contradictory. Vitamin D_3 and vitamin D analogs significantly induced the expression of Bcl-2 in psoriasis (Adisen et al., 2006). However, Xu et al. (1993) reported that vitamin D_3 protected HL60 cells against apoptosis but down-regulated the expression of the Bcl-2 gene. Wagner et al. (2003) found that vitamin D_3-induced apoptosis of Y79 cells was accompanied by a reduction of Bcl-2 and increase of Bax protein.

A recent study further determined that Bcl-2 inhibits autophagy by repressing calcium signals, depending on Bcl-2's location. Bcl-2 inhibits autophagy only when Bcl-2 resides in the ER, where it has been suggested to regulate cellular Ca^{2+} homeostasis (Hoyer-Hansen et al., 2007). To fully understand the relationships between VDR and Bcl-2, all Bcl-2 family members need to be investigated.

2. Vitamin D_3 regulates nucleation through beclin-1 and PI3KC3

Beclin-1 sits at the core of autophagy regulation (Sun et al., 2009). It is a key component of the PI3KC3 complex, which is important for the localization of autophagic proteins to a pre-autophagosomal structure (Kang et al., 2011; Kihara et al., 2001). Beclin-1 is regulated by many factors, such as Bcl-2 (Pattingre et al., 2005), NF-κB (Copetti et al., 2009b), vitamin D_3, and vitamin D3 analogs (Hoyer-Hansen et al., 2005; Wang et al., 2008; Yuk et al., 2009). Inhibition of the VDR target gene cathelicidin significantly weakens vitamin D_3-enhanced beclin-1 expression and vitamin D_3-induced autophagy (Wang et al., 2008; Yuk et

al., 2009). However, the mechanism by which vitamin D_3 increases beclin-1 expression remains unclear.

Vitamin D_3 can also increase beclin-1 expression through Bcl-2. Beclin-1 is a Bcl-2-homology-3 (BH3)-only protein (Sinha and Levine, 2008). Bcl-2 binds directly to a BH3 domain in beclin-1, inhibiting beclin-1 and consequently autophagy. Silencing of endogenous Bcl-2 increases the level of starvation-induced autophagy, possibly due to the release of beclin-1 from the Bcl-2-beclin-1 complex, allowing a sufficient amount of beclin-1 to be recruited to bind to PI3KC3 (Maiuri et al., 2007; Pattingre et al., 2005; Zhang et al., 2009).

Besides its effects on beclin-1, vitamin D_3 signaling activates PI3K signaling pathway to induce autophagy. PI3K represents a family of kinases that phosphorylate the 3-hydroxyl group in phosphatidylinositol inositides (Saji and Ringel, 2010). Vitamin D_3 activates the PI3K pathway in THP-1 cells (Sly et al., 2001), enhances the expression of beclin-1, and induces the expression of PI3KC3 in leukemia cells (Wang et al., 2008).

3. Vitamin D_3 increases lysosome function to promote maturation and degradation

Cathelicidin, a VDR downstream gene, is essential in autophagosome formation. Cathelicidin is recruited into autophagosomes through the Ca^{2+}/calmodulin-dependent kinase (kinase-beta) and AMP-activated protein kinase signaling pathways in human monocytes treated with vitamin D_3 (Yuk et al., 2009).

VDR also regulates autophagy through $p19^{INK4D}$. $p19^{INK4D}$ is a cyclin-dependent kinase inhibitor. Vitamin D_3 induces the expression of $p19^{INK4D}$ in SCC25 cells, thus protecting cells from autophagy-induced death (Tavera-Mendoza et al., 2006). It is clear that vitamin D_3 signaling increases $p19^{INK4D}$ which in turn decreases autophagy and decreases VDR bound to the promoter of the $p19^{INK4D}$ gene (Tavera-Mendoza et al., 2006). However, the mechanism of $p19^{INK4D}$ function in autophagy still remains largely unclear.

Vitamin D analog EB1089 can increase the volume of the acidic compartment of lysosomes and the protease activity of lysosomes in a time-dependent manner starting before any apparent changes in cell morphology or DNA fragmentation are detectable (Hoyer-Hansen et al., 2005). Therefore, vitamin D_3 signaling can enhance autolysosome maturation and degradation.

Vitamin D/VDR Regulation of Inflammatory Signaling in Autophagy

Inflammation (*inflammare* in Latin, to set on fire) is the body's immediate response to damage to its tissues and cells by pathogens, noxious stimuli such as chemicals, or physical injury (Weiss, 2008; Medzhitov, 2008). Both autophagy and VDR signaling play critical roles in controlling inflammatory responses. Below we discuss in more depth the inflammatory signaling pathways associated with vitamin D and/or autophagy.

1. NF-κB affects nucleation through beclin-1

The nuclear factor-κB (NF-κB) family plays diverse roles in immunity, inflammation, and cancer (Karin, 2006). VDR down-regulates NF-κB activity (Wu et al., 2010a; 2010b). A NF-κB binding site is found in the promoter of the beclin-1 gene (Copetti et al., 2009b). Active NF-κB p65 up-regulates the expression of beclin-1 and stimulates autophagy in several cellular systems (Copetti et al., 2009a).

Constitutively active IκB kinase (IKK) subunits stimulate autophagy. Inhibition or ablation of NF-κB p65 fails to suppress IKK-induced autophagy (Criollo et al., 2010). At this point,

it is clear that vitamin D_3 signaling decreases autophagy through NF-κB. However, the effects of NF-κB on autophagy are inconsistent.

In contrast to the stimulatory role of NF-κB in the regulation of autophagy, NF-κB has emerged as a negative regulator of autophagy, as induced by tumor necrosis factor, reactive oxygen species (ROS), and starvation in some cell lines (Djavaheri-Mergny et al., 2006). NF-κB inhibits starvation-dependent autophagy in the acute myeloid leukemia (AML) cell line U937 (Fabre et al., 2007). Prolonged NF-κB activation prevents *E. coli*-induced autophagy in macrophages by down-regulating the expression of Atg5 and beclin-1 (Schlottmann et al., 2008). Further research in various systems will be required to fully clarify the roles of NF-κB in autophagy.

2. Vitamin D_3 may inhibit tumor necrosis factor-alpha (TNF-α) in autophagy

TNF-α is a pleiotropic inflammatory cytokine produced by activated immune cells as well as stromal cells (Esposito and Cuzzocrea, 2009). TNF-α significantly increases the expression of beclin-1 through the JNK pathway in human atherosclerotic vascular smooth cells (Jia et al., 2006). Vitamin D_3 inhibits TNF-α in mycobacteria-infected macrophages and peripheral blood mononuclear cells from pulmonary tuberculosis patients (Martineau et al., 2007; Prabhu Anand et al., 2009). The vitamin D analog cholecalciferol reduces the circulating level of TNF-α (Stubbs et al., 2010). In addition, TNF-α significantly increases the expression of *MAP1LC3* (ATG8) to induce autophagy. *MAP1LC3* expression is induced via both the Akt and JNK pathways in human atherosclerotic vascular smooth cells (Jia et al., 2006). Therefore, vitamin D3 signaling may decrease TNF-α-induced autophagy.

3. NOD2 recruits ATG16 to regulate elongation

NOD2 is an intracellular pattern recognition receptor that recognizes muramyldipeptide (MDP), an integral component of bacterial cell walls. NOD2 is expressed in myelomonocytic cells, dendritic cells, and intestinal epithelial cells (Lecat et al., 2010). NOD2 triggering by MDP induces autophagy in dendritic cells. This effect requires receptor-interacting serine-threonine kinase-2, ATG5, ATG7, and ATG16L1 (Cooney et al., 2010). Vitamin D_3 robustly stimulates the expression of the NOD2 gene and protein in primary human monocytic and epithelial cells (Wang et al., 2010). Moreover, NOD2 is known to trigger autophagy and eliminate intracellular bacteria through the recruitment of ATG16L1 to the site of bacterial entry (Travassos et al., 2010). Therefore, vitamin D_3 may increase vesicle elongation through the NOD2 pathway.

4. Autophagy via Interferon-gamma (IFN-γ)

IFN-γ is a cytokine produced by lymphocytes that has antiviral, immunoregulatory, and anti-tumor properties (Schroder et al., 2004). Vitamin D_3 inhibits IFN-γ in naive CD62 ligand$^+$CD4$^+$ T cells (Staeva-Vieira and Freedman, 2002) and mycobacteria-infected peripheral blood mononuclear cells and macrophages (Martineau et al., 2007; Prabhu Anand et al., 2009). IFN-γ activates and increases lysosome activity in macrophages. It directly induces autophagy and the recruitment of autophagy proteins to the mycobacterial phagosome in macrophages (Al-Zeer et al., 2009; Gutierrez et al., 2004; Singh et al., 2006). Autophagy induced by IFN-γ depends on ATG5 (Chang et al., 2010). IFN-γ activation of macrophages also induces nitric oxide production, which in turn promotes autophagy through an autocrine positive-feedback loop (Ghadimi et al., 2010). IFN-γ level increases when cells are under certain stresses, such as *Salmonella* infection (Liu et al., 2010). However, there is no direct evidence to show that vitamin D_3 signaling may decrease autophagy through IFN-γ.

Overall Functions of Vitamin D_3 Signaling in Autophagy Homeostasis

Vitamin D_3 signaling affects autophagy at several levels, the outcome of which is two-sided (Figure 2). On one hand, vitamin D_3 signaling increases the level of free cytosolic calcium and consequently decreases mTOR activity and induces autophagy; vitamin D_3 signaling also increases beclin-1 through several pathways, decreases the inhibition of Bcl-2, increases cathelicidin, and down-regulates NF-κB, which may decrease beclin-1 level. Vitamin D_3 signaling can increase PI3KC3 protein, enhancing nucleation. To promote elongation, vitamin D_3 signaling increases NOD2 level to recruit ATG16, increases lysosomal protease activity, and induces autophagosomes to fuse with lysosomes through cathelicidin.

On the other hand, vitamin D_3 signaling may decrease autophagy through different mechanisms, especially under certain stresses. Vitamin D_3 may decrease the level of NF-κB, TNF-α, or IFN-γ, thus decreasing autophagy. In addition, vitamin D_3 increases the level of $p19^{INK4D}$, which protects cells from autophagy-induced death (Figure 2).

Vitamin D, VDR, and Macroautophagy in Inflammation and Infectious Disease

Acute inflammation is considered a host defense strategy to remove the injurious stimuli. Inflammation plays a critical role in wound healing and infection resolution. Inflammation is not a synonym for infection. Infection is caused by an exogenous pathogen, such as bacteria, viruses, and parasites, whereas inflammation is one of the host responses to the pathogen.

Although a successful inflammatory response is normally closely regulated by the body, inflammation could become pathologic and out of control. If the acute inflammation fails to eliminate the pathogen, the inflammatory process persists and acquires new characteristics (Medzhitov, 2008). Chronic inflammation is a prolonged, dysregulated, and maladaptive response that involves active inflammation, tissue destruction, and attempts at tissue repair (Weiss, 2008). Compelling evidence demonstrates that both vitamin D signaling and autophagy play a critical role in the pathogenesis of chronic inflammation and infection.

1. Vitamin D signaling and autophagy in inflammatory bowel diseases

Inflammatory bowel disease (IBD) is a dysregulated response of the immune system associated with intestinal tissues to the commensal microbiota in a genetically susceptible host (Kaser and Blumberg, 2008). The major types of IBD are Crohn's disease (CD) and ulcerative colitis. The pathogenesis of IBD involves a complex interplay between genetic, microbial, immunological, and environmental factors (Bouma and Strober, 2003). More than 30 genetic loci associated with IBD have been identified in genome-wide association studies (Schreiber, 2009). Autophagy-associated genes *ATG16L1* and *IRGM* are confirmed susceptibility loci for CD (Hampe et al., 2007; Parkes et al., 2007; Rioux et al., 2007). Variants in the *NOD2* locus are associated with the strongest risk of developing CD (Hugot et al., 2001).

Mucosal inflammations in patients with IBD are accompanied by elevated levels of activated NF-κB, particularly p65 (Rogler et al., 1998; Schreiber et al., 1998). NOD2 and NF-κB play important roles in regulating autophagy. Paneth cells play an important role in intestinal innate immunity by means of secreting granule contents, including antimicrobial peptides and lysozyme (Ouellette, 2010). In experimental models, Paneth cells show notable abnormalities in the granule exocytosis pathway in *ATG5*- and *ATG16L1*-deficient mice (Cadwell et al., 2008). In human study, *NOD2* mutations have been largely linked to ileal CD and have been associated with reduced expression of α-defensins HD-5 and HD-6 in

isolates of ileal Paneth cells (Wehkamp et al., 2004). Taken together, the data strongly implicate autophagy in the pathogenesis of IBD (Kaser and Blumberg, 2008).

Deficiency of vitamin D_3 has been suggested as an important environmental factor for IBD (Laverny et al., 2010). Vitamin D_3 signaling regulates autophagy through several steps, which may affect the efficacy of treatments with vitamin D_3 and its analogs on IBD. Vitamin D_3 can increase NOD2 expression in human intestinal epithelial cells (Wang et al., 2010). In rabbits that were given a plant containing high levels of vitamin D_3 for 15 or 30 days, time- and dose-dependent increases in the size and number of Paneth cells were found in the jejunum (Zanuzzi et al., 2008). In a pilot clinical study in IBD patients, Miheller et al. (2009) reported a short-term beneficial effect on Crohn's disease activity after one-year administration of vitamin D_3. However, there is no direct in vivo evidence of vitamin D_3 signaling in the regulation of autophagy in IBD.

2. Vitamin D, autophagy, and infectious diseases

Some microorganisms have developed mechanisms to counteract or take control of the autophagic pathway as a survival strategy (Colombo et al., 2006; Kirkegaard et al., 2004). *Coxiella burnetii* resides in a phagosome that interacts with autophagic vacuoles and then with lysosomes to generate a large replicative niche. This bacterially driven interaction with autophagosomes and its transit through the autophagic pathway favor Coxiella replication in the host cell. We speculate that vitamin D_3 signaling may inhibit autophagy and kill the bacteria through cathelicidin. However, we found no published reports on the effects of vitamin D_3 signaling and *Coxiella burnetii*.

Cathelicidins are one of the major antimicrobial peptide families. In human, there is only one cathelicidin family member, human cationic antimicrobial protein (hCAP-18), which is cleaved to release LL37 (Durr et al., 2006). LL-37 has shown a broad spectrum of activity against both Gram-negative and Gram-positive bacteria, various viruses, and fungi (Tjabringa et al., 2006). In humans, cathelicidin contains activating VDREs in its promoter region, 507 bp upstream of its transcription initiation site (Wang et al., 2004). Activation of VDR results in the expression of cathelicidin at both the mRNA and protein levels in monocytes/macrophages (Liu et al., 2006; Peric et al., 2008; Wang et al., 2004).

There is a long history of using vitamin D to treat mycobacterial infections (Liu and Modlin, 2008; Hewison, 2010). Vitamin D_3's antagonism of *M. tuberculosis* involves antimicrobial peptides (Liu et al., 2006) and autophagy (Yuk et al., 2009). Vitamin D_3-induced antimicrobial activity is completely inhibited in the presence of siRNA against cathelicidin (Liu et al., 2007; Yuk et al., 2009). Hence, cathelicidin is essential for the induction of autophagy by vitamin D_3 in bacterial infection.

Conclusion and Future Directions

Increasing evidence supports the idea that autophagy is regulated by vitamin D_3 signaling at different levels, including induction, nucleation, elongation to maturation, and degradation. Vitamin D_3 signaling plays essential roles in regulating autophagy to avoid autophagy-induced damage and to inhibit invasion of microorganisms.

To understand the effects of vitamin D_3 and autophagy in inflammation and infectious diseases, we need to explore mechanisms by which vitamin D_3 signaling regulates autophagy, especially in disease-associated experimental models in vivo. The unknown questions include: 1) the relationships between VDR and Bcl-2; 2) the mechanism by which vitamin D_3 increases beclin-1 expression; 3) the mechanism by which $p19^{INK4D}$ decreases autophagy; 4) the effects of NF-κB on autophagy; 5) whether vitamin D_3 signaling is

directly involved in the regulation of autophagy in IBD; and 6) bacterial-host interactions by which bacteria use autophagy as a survival strategy. Studies on the above aspects will improve our understanding of the functions of vitamin D_3 signaling and apply the insights to the development of effective therapy in anti-inflammation and anti-infection.

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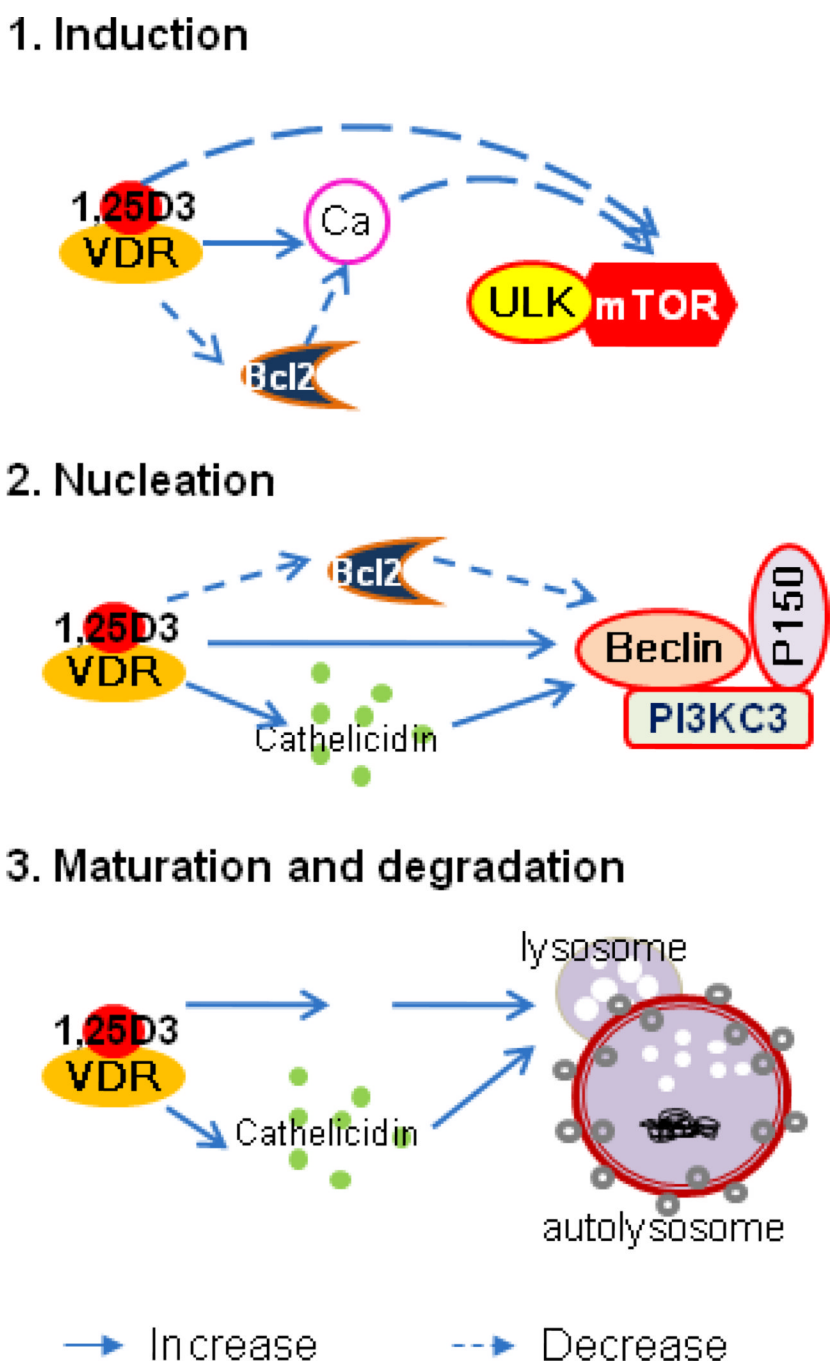

Figure 1.
Vitamin D_3 regulation of autophagy at different levels. 1. Induction: Inhibits mTOR by increasing free calcium to induce autophagy. 2. Nucleation: Increases Beclin 1 and PI3K3 to induce autophagy. 3. Maturation and degradation: Increases lysosome to increase autophagy.

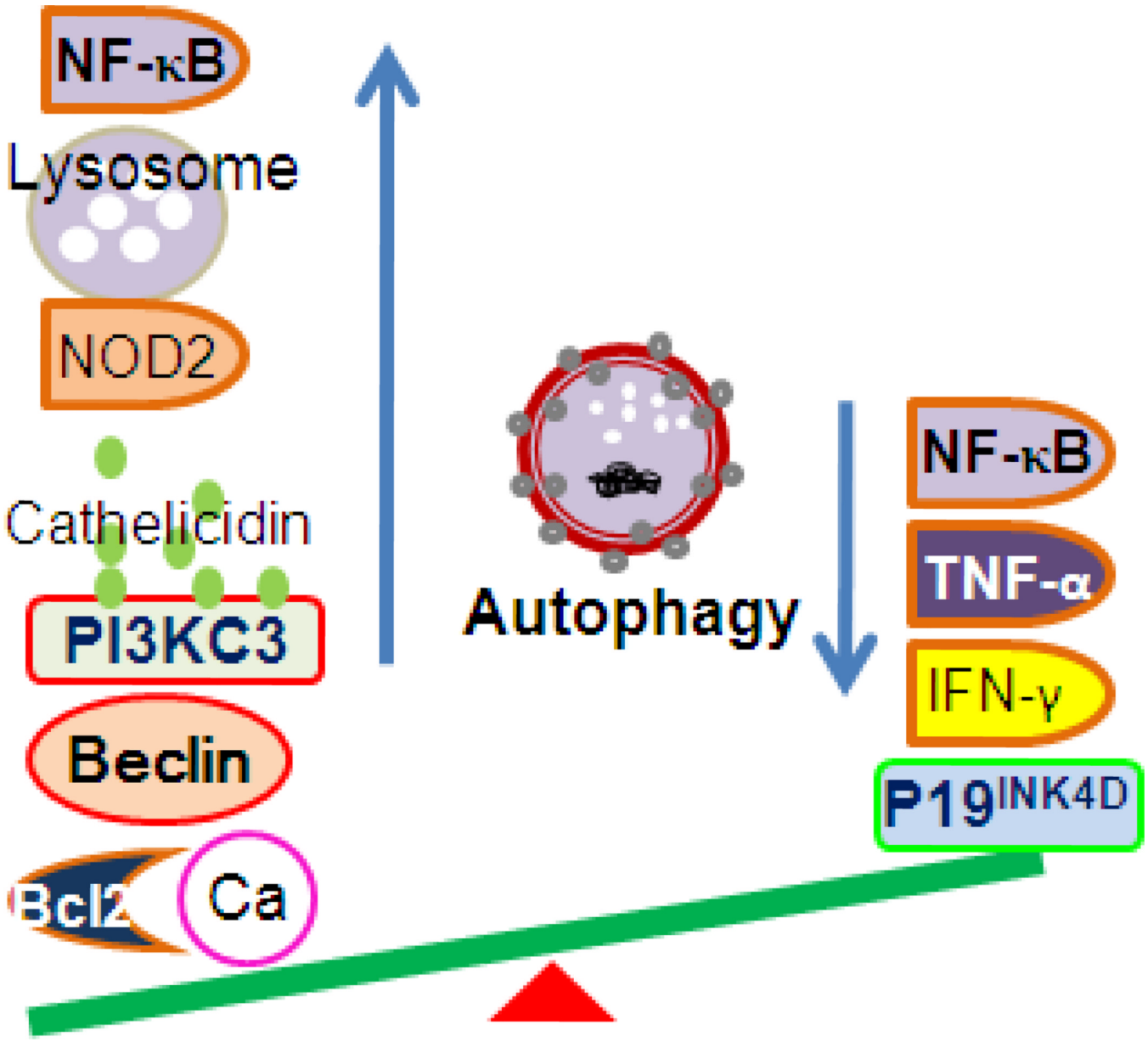

Figure 2.
Vitamin D_3 signaling regulates autophagy homeostasis. Vitamin D_3 signaling may increase autophagy through the following factors: elevated cytosolic calcium; Beclin 1, cathelicidin, and PI3KC3; and NOD2, lysosomal protease activity, and decreased NF-κB activity. Vitamin D_3 signaling may decrease autophagy through the following regulators: $P19^{INK4D}$, activation of NF-κB, TNF-α, and IFN-γ.

Table 1

Related Pathways Involved Autophagy Induction by Vitamin D Compounds

Related Pathway	Experimental System	Actions of Vitamin D and Its Analog
mTOR	human myeloid leukemia cells (HL60)	Decrease mTOR protein level to induce autophagy (Wang et al., 2008)
Calcium	Human breast carcinoma (MCF-7, MCF10A)	Increase free cytosolic calcium to inhibit mTOR and induce autophagy (Hoyer-Hansen et al., 2007)
Bcl-2	MCF-7	Decrease inhibition of Bcl-2 on Beclin 1 to induce autophagy; decrease endoplasmic reticulum Bcl-2 to increase calcium to induce autophagy (Hoyer-Hansen et al., 2007)
Beclin 1	MCF-7, HL60, human primary monocytes/macrophages, human monocytes THP-1	Increase Beclin 1 to induce autophagy (Hoyer-Hansen et al., 2005; Wang et al., 2008; Yuk et al., 2009)
PI3KC3	HL60	Increase PI3KC3 to induce autophagy (Wang et al., 2008)
Cathelicidin	THP-1	Increase cathelicidin to increase Beclin 1, promote lysosome to fuse with autophagosome, increase autophagy (Yuk et al., 2009)
Cyclin-dependent kinase (CDK) inhibitor $p19^{INK4D}$	Human head and neck squamous cell carcinoma (SCC25)	Decrease $p19^{INK4D}$ to increase autophagy (Tavera-Mendoza et al., 2006)
N/A	MCF-7	Increase radiation-induced autophagy (Demasters et al., 2006)
N/A	Murine macrophages (Raw 264.7)	Increase autophagy (Yuk et al., 2009)

Note: N/A, not discussed in this article.