Autophagy exists in 3 separate forms: microautophagy, chaperone-mediated autophagy, and macroautophagy. Each of these pathways has been reviewed extensively.1–3 Most laboratory studies have concentrated on the process of macroautophagy, and for the sake of this review, we will use the more general term autophagy to denote this specific process. Although first described in mammalian cells, the genetic and molecular bases of autophagy were initially characterized in yeast.4 In that context, several autophagy-related (ATG) genes were identified that seem essential for the formation of the autophagosome, or for the subsequent fusion of the autophagosome with the vacuole (the yeast equivalent of the lysosome).5 Most of these gene products have been well conserved in evolution, which suggests that autophagy plays an essential role in organismal survival. On a general level, autophagy seems essential both to maintain cellular homeostasis (via the removal of damaged protein and organelles) and to provide a survival mechanism for cells during stress. Autophagic flux (ie, an increase in both the formation of autophagosomes and the autophagosome fusion with the lysosome) is regulated by both extracellular and intracellular cues in an effort to promote prosurvival pathways, whereas minimizing destruction of proteins and organelles required for cell survival.6 The classic stress is nutrient/amino acid deprivation, where the induction of autophagy seems to provide the cell with biosynthetic intermediates that are not available from the environment. Nonetheless, it is now clear that multiple different forms of stress can induce a rise in autophagic flux.7,8

With the growing interest in autophagy, it now seems that this process affects every organ system and modulates an expanding list of disease processes.3 Within the cardiovascular system, most work has centered on the role of autophagy in angiogenesis effect autophagy endothelial cells.
Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Aβ</td>
<td>β-amyloid</td>
</tr>
<tr>
<td>ATG</td>
<td>autophagy-related genes</td>
</tr>
<tr>
<td>BMPR2</td>
<td>bone morphogenetic protein receptor type-II</td>
</tr>
<tr>
<td>eNOS</td>
<td>endothelial nitric oxide synthase</td>
</tr>
<tr>
<td>MTOR</td>
<td>mechanistic target of rapamycin</td>
</tr>
<tr>
<td>NO</td>
<td>nitric oxide</td>
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<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
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<tr>
<td>VSMC</td>
<td>vascular smooth muscle cells</td>
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<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
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<tr>
<td>WPB</td>
<td>Weibel–Palade body</td>
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the myocardium. Nonetheless, there is a small but growing body of literature attempting to understand how normal and abnormal autophagy has an effect on vascular pathophysiology. Here, we review this body of literature with particular emphasis on how autophagy regulates the biology of endothelial and vascular smooth muscle cells (VSMCs).

Stimulation of Vascular Autophagy by Oxidized Lipids and β-Amlyoid

Emerging evidence suggests that the induction of endothelial autophagy may play an important role in the cellular response to various important stressors and triggers linked to disease (Figure 1). For instance, using primary rat aortic smooth muscle cells, it was observed that lipid peroxides, such as 4-hydroxynonenal stimulate autophagosome production potently. Furthermore, the removal of 4-hydroxynonenal–modified proteins from smooth muscle cells is inhibited by treatment with 3-methyladenine, an autophagy inhibitor. In contrast, pre-treatment with rapamycin, a mechanistic target of rapamycin (MTOR) inhibitor that stimulates autophagic flux, accelerates the removal of 4-hydroxynonenal–modified proteins. The induction of autophagy seems to be cytoprotective in this setting because autophagy inhibition seems to augment cell death of smooth muscle cells exposed to lipid peroxides. Recent studies have suggested that autophagic induction is mediated, in part, by the activation of the endoplasmic reticulum (ER) stress response. It is well known that lipid peroxides can modify proteins, which in turn, can accumulate within the ER and subsequently stimulate the ER stress response. Recent evidence suggests that this stress response leads to increased autophagy, through a mitogen-activated protein kinase/Jun N-terminal kinase–dependent signaling pathway. The role of autophagy in macrophage lipid homeostasis is also receiving increased attention (Figure 2). The ability of macrophages to store cholesterol esters in large lipid droplets gives rise to the classic foam cell that makes an important contribution to atherosclerotic plaque formation and instability. It was generally assumed that within macrophages, neutral cytoplasmic lipases were responsible for lipid droplet breakdown. This degradation is required for cholesterol efflux and for the important process of reverse cholesterol transport. However, it is now apparent that lipid droplets can also be cleared in an autophagy–dependent process, wherein lipid droplets are delivered to the lysosome, where they undergo subsequent lysosomal acid lipase–dependent lipolysis. This process was first described in

![Figure 1. Stimulation of autophagy occurs through mechanistic target of rapamycin (MTOR)–dependent and MTOR–independent pathways within vascular cells. Complex I of MTOR (mTORC1) is a well characterized, negative regulator of autophagosome formation. The classical autophagic stimulus of nutrient withdrawal is thought to be largely transduced through this pathway, whereas the pharmacological agent, rapamycin, works as an inhibitor of MTOR, thereby relieving the tonic autophagic-inhibition of MTORC1. Other agents, such as endoplasmic reticulum (ER) stress, reactive oxygen species (ROS), and oxidized lipids seem to largely work through a mix of both MTOR–dependent and MTOR–independent pathways, although the precise mechanism of action for these stimuli is largely unknown (illustration credit: Ben Smith).](http://circres.ahajournals.org/)

![Figure 2. Lipid metabolism in macrophages involves autophagy. Evidence suggests that lipid droplets within macrophages can be engulfed by autophagosomes. After fusion with lysosomes, lysosomal acid lipases (purple triangles) can degrade the lipid contained within the autophagosome, contributing to cholesterol efflux from the macrophage. The physiological importance of this pathway is highlighted by the observation that conditional deletion of essential autophagy genes within macrophages exacerbates atherogenesis (see text for details; illustration credit: Ben Smith).](http://circres.ahajournals.org/)
the context of the liver and is known as lipophagy, 16 that is, the selective degradation of lipid droplets through the autophagic machinery. The physiological significance of macrophage autophagy was underscored by analyzing mice with conditional deletion of Atg5 within this specialized cell type. 17,18 This analysis demonstrated that the absence of macrophage autophagy results in significantly increased atherosclerotic plaque formation. These results have, therefore, given impetus to the idea that stimulating autophagy might provide an atheroprotective benefit. 19 Such hopes are also bolstered by observations from previous studies, in which pharmacological inhibition of the MTOR pathway was studied. One of the effects of MTOR inhibition is that it augments autophagic flux, and as such, it is encouraging that this approach has been noted to have clear beneficial effects in various animal models of atherosclerosis. 20,21

Another pathological stimulus that has been linked to autophagic induction is the response of endothelial cells to β-amyloid (Aβ). It is well established epidemiologically that vascular dysfunction and disease can contribute to the progression and to the severity of neurological conditions, such as Alzheimer disease. 22 The brains of patients with Alzheimer disease demonstrate plaques that are, in part, composed of APP/Aβ. Many patients also develop vascular amyloid deposits where there seems to be an accumulation of a fragment of Aβ composed of the protein’s first 40 amino acids (Aβ1–40) within the small vessels of the brain. 23 How the vasculature responds to Aβ exposure is, therefore, of potential clinical relevance. In this regard, it has been demonstrated that Aβ1–40 inhibits the proliferation of human brain vascular endothelial cells. 24 In contrast, a scrambled peptide containing the same amino acids in reverse (Aβ40–1) has no effect on endothelial growth. Using a variety of approaches, it was demonstrated that after Aβ1–40 exposure, there was a marked increase in autophagic flux. Moreover, treatment of Aβ1–40–exposed endothelial cells with the autophagy inhibitor 3-methyladenine restores a near normal level of endothelial proliferation. Using ex vivo hippocampal slices, the authors were able to demonstrate that Aβ1–40 exposure induces an increase in autophagic-positive cells with a corresponding reduction in new vascular growth. 24 This raises the possibility that the coupling between vascular disease and neurological degeneration may occur, at least in part, by APP/Aβ–stimulated induction of endothelial autophagy. In the context of these studies, this induction of endothelial autophagy results in impaired cell growth and vascular regeneration. Although data from human patients are sparse, there are some immunohistochemical studies that have detected evidence of increased autophagy in the endothelium of small brain blood vessels when autopsy specimens from patients with Alzheimer disease were examined. 25 The degree of endothelial autophagic activation seemed to be correlated with the distance from Aβ deposition. These human studies, therefore, again suggest that vascular autophagy may play a role in modulating Alzheimer disease progression.

**Autophagy and Endothelial Function**

There is a growing body of literature that suggests that loss of autophagy may be a central mechanism through which risk factors elicit endothelial dysfunction, and that autophagy may be involved in the regulation of nitric oxide (NO) bioavailability. For example, in endothelial cells, shear stress–induced increases in endothelial nitric oxide synthase (eNOS) phosphorylation and NO production are markedly blunted in autophagy-deficient cells. Coincident with a reduction in NO, loss of autophagy promotes an increase in endothelial reactive oxygen species (ROS) and inflammatory cytokine production, suggesting that autophagy may regulate shear stress–induced vascular homeostasis, in part, through an eNOS–dependent pathway. 26 These data have recently been confirmed using an ex vivo model of steady laminar shear stress, wherein autophagy inhibition (with 3-methyladenine) inhibits eNOS expression, whereas autophagy stimulation (with rapamycin) increases endothelial eNOS expression. 27 Emerging evidence also suggests that endothelial autophagy might modulate the uncoupling of eNOS (with an increase in superoxide versus NO production). For example, CAV1/caveolin-1, a critical determinant of eNOS coupling and NO bioactivity, is also a key regulator of endothelial autophagy. 28 Similarly, recent data also suggest an important role of intracellular NO in the regulation of mitophagy, the more selective process involving autophagic degradation of mitochondria. 6

Another potential link between autophagic flux and endothelial function comes from recent studies involving angiotensin-II. It is well established that angiotensin-II contributes to the development of a diverse array of vascular pathologies. Recent evidence suggests that autophagy may limit the detrimental effects of angiotensin-II on endothelial dysfunction. 29 Another important cardiovascular risk factor, namely diabetes mellitus, elicits vascular injury through diverse mechanisms, including hyperglycemia, augmented angiotensin-II production, and increased oxidative stress. It may, therefore, be clinically relevant that preliminary in vitro studies point toward a protective effect of autophagy in limiting glucose-induced endothelial damage. 30

Interestingly, the potential cardiovascular benefit of certain nutraceuticals and common supplements has also been linked to an upregulation of endothelial autophagy. For example, resveratrol, the main presumptive cardioprotective ingredient in red wine, was recently demonstrated to attenuate endothelial cell inflammation via induction of autophagy. 31 Similarly, vitamin D was recently shown to elicit cytoprotective effects in the endothelium via augmenting autophagic flux. 32

Significant attention has recently focused on the role of micro-RNAs in the maintenance of vascular control. Interestingly, in this regard, MIR216A has been shown to be induced during endothelial aging, and is thought to regulate endothelial homeostasis through a direct interaction with key autophagy genes. 33 In addition, MIR130A promotes survival of endothelial progenitor cells, again, via the targeting of important autophagy genes. 34 In addition, autophagy per se is essential for the biogenesis of microRNAs. This occurs through the establishment of a checkpoint that enables miRNA biogenesis to be sustained by promoting the autophagic removal of inactive DICER1–AGO2 complexes. 35

**Autophagy, Extracellular Matrix, and Angiogenesis**

The biology of endothelial cells is dramatically influenced by their interaction with the extracellular matrix. Indeed, the extracellular matrix is a critical regulator of the survival, proliferation, and migration of endothelial cells. 36 Decorin is a...
secreted matrix proteoglycan that belongs to a large family of similar molecules known as small leucine-rich proteoglycans. These secreted molecules have multiple functions, including regulating the bioavailability of growth factors and inhibiting the activity of multiple cell surface receptors. Of note, treatment of mouse microvascular dermal endothelial cells with soluble decorin induces a significant increase in autophagosome formation. The authors of these studies were able to subsequently demonstrate that this induction requires the interaction of decorin with KDR/VEGFR2, the plasma membrane receptor for vascular endothelial growth factor. Expression of PEG3/PW1 (paternally expressed gene 3) seems to be an important mediator of decorin-induced autophagy and to act downstream of KDR. PEG3 is an imprinted gene that marks a wide array of adult stem and progenitor cells. Within endothelial cells, PEG3 seems to regulate the expression of the essential autophagy-related genes Becn1/beclin1 (yeast Vps30/Atg6) and Map1lc3a (microtubule-associated protein 1 light chain 3 α or yeast Atg8). Decorin was also shown to inhibit capillary morphogenesis in Matrigel assays and VEGF-induced migration, but it remains unknown whether these inhibitory effects are mediated through the ability of the secreted proteoglycan to stimulate autophagy. Follow-up studies suggested that decorin stimulates autophagy through an AMPK-dependent pathway.

Other soluble matrix proteoglycans seem to also induce endothelial autophagy. This growing list includes endorepellin, a fragment of the heparin sulfate proteoglycan Hspg2/perlecain. Similar to decorin, endorepellin seems to induce autophagy through a PEG3-dependent pathway. Endorepellin has known in vivo antiangiogenic properties. Other endogenous inhibitors of angiogenesis can also induce an increase in observable autophagy, including endostatin, as well as Kringle 5, an antiangiogenic molecule derived from Plg/l-plasminogen. This suggests that induction of endothelial autophagy might be a common mechanism through, which endogenous antiangiogenic molecules exert their effects.

Another link between endothelial autophagy and angiogenesis comes from the analysis of mice deficient in Ak3. These animals have an impaired angiogenic response using a standard subcutaneous Matrigel plug assay. This same study also demonstrated that knockdown of AKT3 induces autophagy in endothelial cells. Interestingly, this induction seemed to be independent of Mortk (a known AKT substrate and target) and instead dependent on Xpo1/Crm1 (exportin 1/Crm1 homolog yeast), the major nuclear export receptor. These data and the observations discussed above suggest a negative correlation between autophagic flux and angiogenesis. The basis for such an association is not entirely clear at this time. One potential clue may come from studies in transformed epithelial cells where using an in vitro wound healing assay, and it was demonstrated that cells at the leading edge of the culture has reduced autophagosome formation when compared with cells at the rear of the wound. Moreover, these investigators were able to demonstrate that mouse embryonic fibroblasts derived from either atg3−/− or atg5−/− mice seemed to have greater migratory potential compared with wild-type mouse embryonic fibroblasts. These effects seem to relate to the autophagic-dependent degradation of surface ITG/integrin receptors. Finally, a recent article has implicated autophagy in tumor angiogenesis, as mice carrying an endothelial-specific deletion of Atg5 seemed to develop smaller tumors after the injection of tumor cell lines. The tumors that did form in these animals lacking endothelial autophagy seemed to be infiltrated by blood vessels that were smaller and more tortuous than in control mice.

In addition to postnatal angiogenesis, autophagy has also been linked to prenatal vascular development. One example occurs from analyzing the vascular remodeling that is seen after placental implantation. During a normal pregnancy, extravillous trophoblasts invade the uterine spiral arteries and replace pre-existing vascular endothelial cells. This process seems to require autophagy-competent trophoblasts. Moreover, soluble ENG/endoglin (that functions as a coreceptor for TGFβ/TGF-β signaling) seems to inhibit trophoblast invasion, at least in part, by suppressing autophagy. Given that ENG seems elevated in women with preeclampsia, these results suggest that defective autophagy might contribute to some aspects of preeclampsia. Another link between autophagy and vascular development has come from analysis of mice deficient in ubr4. This gene product belongs to the family of N-recognins that mediate N-degron-dependent proteosomal degradation of specific proteins. ubr4−/− mice die during embryogenesis because of the absence of normal vascular development. It seems that Ubr4 is primarily expressed in endodermal cells and not in the mesodermal-derived vasculature. In these endodermal cells, the absence of Ubr4 causes a marked defect in autophagic flux. It is probable that in a paracrine fashion via autophagic degradation, Ubr4-positive cells generate the nutrients (in this case amino acids) required for vascular development.

**Autophagy and Smooth Muscle Biology**

Although the results with Ubr4-deficient mice demonstrate the role of autophagy in bulk lysosomal-mediated degradation for nutrient supply, autophagy is also important for degradation of specific proteins that have important biological activity. A mutation in the gene encoding bone morphogenetic protein (Bmp) receptor type-II (Bmpr2) represents the most common cause of inherited form of idiopathic pulmonary hypertension. Analysis has revealed that in various animal models of pulmonary hypertension, Bmpr2 expression is reduced. New evidence suggests that Bmpr2 is internalized from the surface of pulmonary smooth muscle cells and ultimately degraded by autophagy. Agents such as chloroquine, which raise lysosomal pH and thereby block autophagic flux, maintain Bmpr2 on pulmonary smooth muscle cells and thereby protect against the subsequent rise in right ventricular pressures observed in rat models of the disease. Thus, in this context, inhibiting autophagy seems to provide a potential strategy to reduce pulmonary hypertension. In contrast, previous studies have demonstrated that in mouse models of pulmonary hypertension stimulated by chronic hypoxia, as well as in human lung samples, there is histological evidence of increased autophagy. Mice lacking Lc3b (an essential component of the autophagosome) and thereby autophagy-impaired, seem to have augmented hemodynamic response to hypoxia. As such, whether autophagy is detrimental or beneficial in the
development of pulmonary hypertension remains an important but unanswered question.

Autophagy may also be involved in the process of phenotypic switching that VSMCs can undergo. After injury, smooth muscle cells seem to alter the phenotype from the baseline contractile state to a proliferative synthetic state. This process can be stimulated by addition of the peptide growth factor, platelet-derived growth factor (PDGF). The change to the synthetic state is accompanied by the expression of various markers, including expression of SPP1/osteopontin and VIM/vimentin, as well as removal of the pre-existing contractile apparatus. Given the role of autophagy in cellular degradation, it seems reasonable that this VSMC phenotypic transition might require an intact autophagic machinery. Indeed, smooth muscle cells stimulated with PDGF demonstrate an induction of autophagy. Moreover, pharmacological inhibition of autophagy seems to inhibit the ability of PDGF to induce a synthetic phenotype. Confirmation of the importance of these results for in vivo smooth muscle cell biology awaits the generation, and analysis, of the appropriate genetic models. Given the critical role of VSMC in the development and clinical course of atherosclerosis, it would be important to evaluate the role of autophagy in vivo using experimental models of atherosclerosis and rupture.

Another important process in which autophagy may modulate smooth muscle biology is during vascular calcification. It is well appreciated that chronic renal failure is associated with hyperphosphatemia. Phosphate levels seem to correlate with degrees of vascular calcification and are important contributors to the high mortality seen in patients with end-stage renal disease. Using an in vitro system of calcification, it was shown that exogenous phosphate stimulates autophagy in VSMC. This induction seems to be a result of phosphate-induced mitochondrial ROS production because it can be inhibited by genetic or pharmacological scavenging of oxidants. Interestingly, previous observations in the setting of starvation have suggested a link between mitochondrial ROS production and autophagic flux. The authors also observed evidence for increased autophagy in the vessel walls of rats with elevated serum phosphate levels that again seems to be sensitive to antioxidant intervention. Pharmacological inhibition of autophagy increases calcification, whereas agents that increase autophagy seem to reduce calcification. This mechanism may also provide an explanation for the clinical observation that statins can slow or prevent vascular calcifications. Treatment of VSMCs with atorvastatin results in an induction of autophagy and a suppression of TGFB-stimulated calcification.

Animal Models of Altered Vascular Autophagy

The development of animal models with impaired or absent autophagy should allow for a better understanding of the physiological role of autophagy in vascular biology. In general, the complete absence of autophagy, such as whole body deletions of Atg5 or Atg7, results in rapid postnatal death. Nonetheless, tissue-specific deletion of these essential genes, such as previously discussed in the context of conditional deletion of Atg5 within macrophages, often results in mice that are viable. Nonetheless, although instructive, the complete absence of autophagic flux results in the massive accumulation of damaged and modified proteins and organelles, and as such represents an extreme example that is unlikely to be replicated under normal physiological or even pathological circumstances. As such, future development of additional animal models, where there are more nuanced gain and loss of autophagic function, will undoubtedly be useful.

An initial description of the physiological effects after conditional deletion of Atg5 and Atg7 within mouse endothelial cells has been recently described. These mice are viable, with no obvious outward phenotype. Interestingly, these animals seem to have a defect in the secretion of vWF (von Willebrand factor homolog). The biosynthetic pathway of vWF is complex and involves various post-translational modifications in the ER and Golgi, followed by assembly into discrete structures known as Weibel–Palade bodies (WPBs). Electron micrographs reveal that in endothelial cells lacking ATG7, the shape of the WPBs are shorter and rounder (Figure 3). This alteration is often seen when there is a defect in processing, especially when the pH of the WPB is not acidic enough. Measurement of the pH of WPBs in control or autophagy-deficient endothelial cells reveals that in the absence of autophagic flux, WPBs develop a more alkaline pH. Although the total level of endothelial vWF protein is similar, the packaging of vWF into functional WPBs seems to be reduced in the absence of ATG7. This presumably contributes to an impaired ability to secrete vWF into the plasma when mice lacking endothelial ATG5 or ATG7 are challenged with epinephrine as a secretagogue. Some of these effects observed after genetic deletion of essential autophagy genes could be recapitulated by using chloroquine. Although these results suggest that in the absence of autophagy there is a defect in vWF secretion, it leaves open the precise mechanism underlying this effect. There is a growing link between autophagy and unconventional protein secretion from cells suggesting that autophagy may have a specific role in WPB secretion. Alternatively, it may be that with disruption of ER and Golgi homeostasis, the processing of vWF is impaired. Similarly, autophagy may be involved in the quality control of the WPB intracellular pool. Consistent with the latter explanation, electron micrographs of control endothelial cells reveal consistent evidence of partially degraded vWF, whereas in autophagy-deficient endothelial cells vWF expression have no clear defect in vascular development within the retina. Whether the angiogenic response after injury is impaired has, however, not been assessed. The WPBs are also a source of other important vasoactive compounds, including EDN1/endothelin-1 and ANGPT/angiopoietin, however, the role of autophagy in the endothelial release of these mediators also remains unclear.

Autophagy and Vascular Aging

The notion that impaired autophagy might contribute to a wide range of vascular pathologies, including atherosclerosis and calcification suggests that autophagy might modulate a shared, global parameter associated with such diseases. The parameter that is most appealing is that rates of autophagy are coupled
to rates of vascular aging. Clearly, age is the major risk factor for cardiovascular disease and autophagy is increasingly being implicated as a modulator of longevity. Indeed, global gain of function approaches demonstrate that autophagy induction can extend murine life span. It is tempting to, therefore, speculate that a decline in vascular autophagy might contribute to what we consider to be the phenotype of the aging vasculature (Figure 4). Such properties include increased stiffening of the large arteries and impaired endothelial-dependent relaxation. The latter property is thought to reflect the effect of higher levels of ROS produced within the aging vasculature. In this context, autophagy, as well as the more selective mitophagy, clearly modulates the overall redox state. Defects in these processes have been increasingly linked to cardiovascular disease exacerbated by oxidative stress. Analysis of endothelial cells from old versus young mice, as well as analysis of endothelial cells from old versus young patients, reveals that older endothelial cells have lower levels of BECN1 and higher levels of SQSTM1/p62. Because SQSTM1/p62 is largely cleared through autophagy, these results are at least consistent with the notion that the aging vasculature has reduced autophagic flux. The notion that this might be more than a correlation is supported by pharmacological interventions that attempt to increase autophagy. The addition of trehalose or spermidine, agents that stimulate autophagy, seems to reverse aspects of arterial aging. The parameters studied in these models included both measures of arterial stiffening and endothelial-dependent function. Finally, there is large literature in both rodent models and human subjects that caloric restriction improves vascular function and potentially slows vascular aging. Given that nutrient availability is the classic regulator of autophagy, it is conceivable that some of the effects of caloric restriction are mediated, at least in part, by the activation of vascular autophagy. Similarly, potentially promising agents, such as resveratrol, an agent thought to mimic caloric restriction, and as mentioned, also known to stimulate endothelial autophagy, has been recently shown to delay aspects of vascular aging in a primate model.
function, presumably because of increased ROS production, the mechanisms underlying vessel aging might be understood finally. Recent studies on vascular autophagy hint that the mechanism is manipulated using knockdown or pharmacological approaches. Going forward, it would be of interest that impaired autophagy is associated with an increase in ROS and an increase in the activation of the inflammasome. It is, perhaps, not a coincidence that the induction of autophagy in endothelial or VSMCs seems to contribute to a host of important diseases ranging from atherosclerosis to pulmonary hypertension. The progress that has been made to date has largely relied on cell culture models, in which autophagy is manipulated using knockdown or pharmacological approaches. Going forward, it would be of importance to complement these observations by developing the corresponding animal models using conventional targeted genetic approaches. As mentioned, it is also intriguing to think that diminished autophagy may play a role in vascular aging. It is of interest that impaired autophagy is associated with both an increase in ROS and an increase in the activation of sterile inflammation, as characterized by activation of the inflammasome.

## Table. A Summary of Some of the Known Alterations on Endothelial, VSMC, or Macrophage Biology After Positive or Negative Manipulation of Autophagic Flux

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Increase or Decrease of Autophagy</th>
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<tbody>
<tr>
<td>VSMC</td>
<td>↑autophagy: ↑[MMP2] expression with ↓[PAS, ↑[VSMC phenotype switching, ↓[vascular calcifications]</td>
</tr>
<tr>
<td>Macrophage</td>
<td>↑autophagy; ↑[atherosclerosis]</td>
</tr>
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Ang-II indicates angiotensin-II; BMPR2, bone morphogenetic protein receptor type-II; NO, nitric oxide; VSMC, vascular smooth muscle cell; and vWF, von Willebrand factor.

## Conclusions

Our knowledge of the role of autophagy in vascular biology is relatively limited at this time. Nonetheless, there are already indications that autophagic flux can be modulated by factors that range from oxidized lipids to extracellular matrix components and from APP/Aβ to serum phosphate (Table). In turn, the induction of autophagy in endothelial or VSMCs seems to contribute to a host of important diseases ranging from atherosclerosis to pulmonary hypertension. The progress that has been made to date has largely relied on cell culture models, in which autophagy is manipulated using knockdown or pharmacological approaches. Going forward, it would be of importance to complement these observations by developing the corresponding animal models using conventional targeted genetic approaches. As mentioned, it is also intriguing to think that diminished autophagy may play a role in vascular aging. It is of interest that impaired autophagy is associated with both an increase in ROS and an increase in the activation of sterile inflammation, as characterized by activation of the inflammasome.

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## Disclosures

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## References


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