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Original Article

Conflict effects of autophagy on cellular senescence in advanced ages: A systematic review

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Abstract

Introduction: Recently, autophagy as a highly conserved catabolic intracellular process is considered a promising therapeutic target, particularly in pathological alternations under aging conditions. This systematic review was designed to qualitatively analyze the interaction between autophagy and aging in various organs of animal models.

Methods: Based on our primary search, 9478 articles were identified, and following the screening, ultimately, 80 full texts were included to proceed with further analysis. Next, using SPSS software, data analysis of autophagy and aging-related markers and autophagy alternation throughout aging, was performed.

Results: Despite debatable results, we established that the most of studies showed that the autophagy process reduced in different aged organs significantly.

Conclusion: The outcomes demonstrated that autophagy induction during aging was inferior to those reports that indicated the therapeutic potential of autophagy. Taken together, it should be considered that autophagy inducers could be counted as anti-aging agents.

Introduction

Autophagy is predominately known as a highly conserved dynamic catabolic process, which permits the recycling of worn-out cellular constituents such as damaged and aggregated misfolded proteins to retain intracellular homeostasis and cellular bio-energetic activities under different stress conditions that ultimately promote cellular aging.[1,2] In addition, this phenomenon is regulated by some autophagic related genes (*Atg*s), as well as specific intracellular proteins, mainly consist of microtubule-associated protein light chain 3 (LC3), beclin-1, and SQSTM1 (p62).[2] According to the previous studies, any pharmacological or genetic intervention could influence the cell destination through autophagic modulation.[3,4] In hence, the fine-tuned regulation of autophagy is highly demanded to ensure the maintenance of cellular hemostasis. However, autophagy as a double-edged sword exhibits both protective and cell death effects during pre-activation and excessive activation under different conditions, including oxidative stress, inflammation, and aging.[5-8] Although aging is not considered a disease solely but could be a significant risk factor and the leading cause of different organs disability; during cellular senescence, a time-dependent deterioration of physiologic functions occurs in all cells and tissues. In better words, all organs are affected by multiple pathological changes such as reactive oxygen species (ROS) generation, oxidative stress enhancement, lipofuscinosis, and fibrosis throughout aging. In addition, some intracellular organelles such as mitochondria biogenesis are modified, particularly by the reduction of peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) expression and acetylation during aging, which promote further ROS production, nuclear factor kappa B (NF-κB) stimulation, and the sequestration of nuclear factor forkhead box protein O1 (FOXO1), as a regulator of ubiquitin proteolysis, and mitophagy process.[9,10] Recently, several scenarios have been elucidated that the aging process directly links to some proteolytic phenomena, including autophagy and the ubiquitin-proteasome system. Increased age leads to a gradual deterioration of functional and structural changes and interstitial fibrosis in different organs. Albeit, there is no debate regarding autophagy participation in aging, the precise role of autophagy in other organs remains to be determined. The current comprehensive review mainly aimed to investigate autophagy modulation, particularly by any intervention beyond the aging-associated defects in different organs. As a secondary outcome, the autophagy-related underlying mechanisms of action during the aging process were evaluated.

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Methods

Search strategy

The initial systematic search was predominantly focused on two keywords, "aging and autophagy", concerning thesaurus terms and free-text terms, Embase, Medline (via PubMed, Ovid) databases. All data obtained from search strategies are brought in Figure 1. Notably, all selected studies during search strategy were both unpublished and published English articles, and the onset date qualified for inclusion consists of 1980-Jan till 2019-Nov. Finally, the findings of this comprehensive review were analyzed qualitatively and presented in a description form.

Inclusion and exclusion criteria

This qualitative review was considered to include all studies that evaluated the interaction between the autophagy process and aging by the measurement of various related markers, as well as autophagic protective/ cell death effects, in animal models. To note, there was not any exclusion based on the type of drug/ chemical agent used for autophagy modulation and the route of administration. The full text of all selected studies that did not qualify according to the inclusion criteria, such as non-English written articles, in vitro experiments, clinical trials, and reports without required standard quality, were ultimately removed.

Data extraction

Two reviewers (FS and NV) screened both relevant titles and abstracts independently, to ascertain eligible articles. Any discrepancy was arbitrated again by a third reviewer (AR). For data extraction, some considered study design items including first author's name, published year, study location, animal type (species, sex), sample size, age of animals, dose and the route of drug or any chemical agent, and autophagy/aging markers were prepared. All required data extraction from the articles were listed in extraction diagrams (Table 1). Endnote software version X9 was used to organize studies-related data and duplicated identification. It is also worthy to note that the corresponding author of any study was contacted to clarify each missing or unclear data, where required.

Abbreviations

A2AR: A2a Receptor; Atgs: Autophagy Related Genes; FOXO: Forkhead box; LC3: Microtubule-Associated Protein Light Chain 3; POCD: Postoperative Cognitive Dysfunction; rAAV: recombinant Adeno-Associated Viral; ROS: Reactive Oxygen Species; SA β-galactosidase: Senescence-Associated Beta-Galactosidase; SIRT3: Sirtuin 3; SQSTM1 Sequestosome 1

Data analysis

Following the data extraction, we used SPSS statistics software, version 16.0 (SPSS Inc., Chicago, III., USA) to delineate some questions, including which countries and in which years authors worked more on autophagy modulation in aged animals, which type of organs used

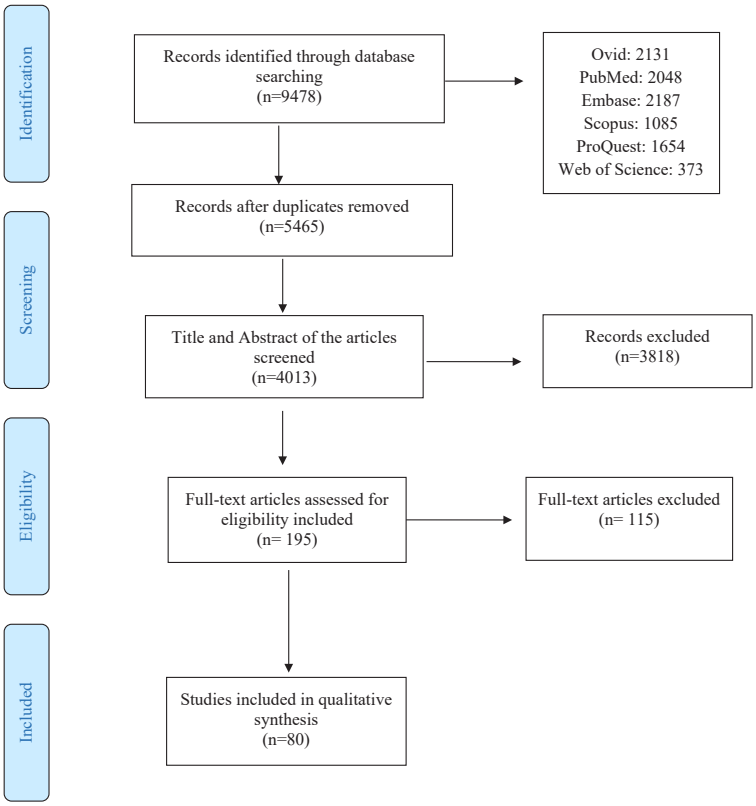

Figure 1. Flow Chart of Systematic Review.

Table 1. The list of data extraction from the articles in extraction diagrams

First author	Publication year	Country	Species and Sex	Age (mon)	N	Tissue	Intervention/drug, dose range (mg/kg)
Ning[11]	2013	China	Male Sprague–Dawley (SD) rats	25	4	Kidney	Short-term calorie restriction
Ott [12]	2016	Germany	C57/BL/6 J Male Mice	18–25	4	Brain	_
Pratiwi[13]	2018	Indonesia	Male Wistar rats	20	10	Skeletal muscle mass	8.1 mg/day/kg body weight
Luo[14]	2013	China	Male Sprague Dawley rats	18–20	9	Skeletal muscle mass	Resistance exercise training
Martínez-Cisuelo[15]	2016	Spain	Male CB6F1 hybrid mice	16	3 to 4	Liver	Rapamycin (14 mg of rapamycin/kg of diet)
Meckes[16]	2017	USA	C57BL/6J mice	28- 30	5	Meniscus and cartilage	Destabilizing the medial meniscus to induce posttraumatic osteoarthritis
Patschan[17]	2014	Germany	Male C57/Bl6N mice	8–12	3	Kidney	Early endothelial outgrowth cells, Bone morphogenetic protein-5
Moruno-Manchon[18]	2016	USA	Female nude mice	4–6	_	Brain	Intraperitoneally injected with Doxil, TFEB overexpression
Puigoriol-Illamola [19]	2018	Spain	Female old SAMP8 Mice	12	6	Brain	RL-118, an 11β-HSD1 inhibitor (21 mg/kg)
Li[20]	2018	China -USA	Old female C57BL/6 mice	8	11	Skin	Caffeine (10 and 20 mg/kg)
Poulose[21]	2011	USA	Male Sprague-Dawley rats	2	5	Brain	High-energy and charge particles induce aging, 16O-particle radiation
Marchesi[22]	2011	Canada	Females proprotein convertase PC5/6 (Pcsk5) inactivated in endothelial cells mice	16-18	3	Heart	_
Manthari[23]	2018	China	Female Kunming mice	17	15	Brain	_
Liu[24]	2018	China	Old male mice	24	3	Kidney	_
Ma[25]	2017	China	Old male C57BL/6J mice	16	3	Bone	Rapamycin 1.5 mg/kg
Liu[26]	2017	China	Male Sprague-Dawley rats	22	4	Liver	Pooled young rats plasma (1 mL, intravenously
Li[27]	2015	China	Male Sprague-Dawley rats	20	4	Brain	1.5% isoflurane inhalation gas
Li Ma[28]	2016	USA-China	Male Fischer 344 rats	22-24	3 to 5	Heart	Isoflurane (ISO, 1MAC), TEMPOL (2 mm)
Mariño[29]	2008	The Netherlands	Zmpste24-Null mice (premature aging mice)	–	6	Heart and skeletal muscle	–
Matsumoto[30]	2018	USA	Mouse strain Mus musculus castaneus possessing short telomeres	12	4 to 15	Heart	_
Lin[31]	2015	China	Wistar–Kyoto rats	22		Carotid arteries	_
Almeida[32]	2017	Brasil	Aged male Lewis rats	9	5	Brain (substantia nigra)	Physical exercise, rotenone 1 mg/kg/day
Ba[33]	2017	China	APPswe/PSEN1dE9 (APP/PS1) mice model of Alzheimer's disease	12	4 to 7	Brain (cortex, hyppocampus)	_
Joseph[34]	2013	USA	Proofreading-Deficient Version of mtDNA polymerase gamma mice (progeroid aging models)	8–15	7 to 9	Skeletal muscle	_
Chen[35]	2014	China	SAMP8 mice	6	6	Brain	β-Asarone 34 mg/kg/day
Chen[36]	2019	China-USA	Male Sprague-Dawley rats	12–15	4 to 5	Brain	Intracranial injection of Mir-497
Carnio[37]	2014	Italy	Muscle-specific Atg7-Null and tamoxifen-inducible muscle-specific Atg7/mice	10 , 22, and 26-	4	Muscle	_
Chen[38]	2019	China	SAMP8	5	4	Brain	20, 40, or 80 mg/kg icariin
Bartolomé[39]	2014	Spain	B-cell–specific deletion of Tsc2 (Btsc22/2) mice	4-10	3 to 8	Pancreas	_
Heather N. Carter[40]	2018	Canada	Male Fisher 344 Brown Norway F1 (hybrid rats)	35–36	5 to 8	Skeletal muscle	Chronic contractile activity
Chen[41]	2016	China	Females and males rats	_	6	Intervertebral disc	Metformin (50 mg/kg/day)
Crupi[42]	2018	USA	C57BL/6J mice	28-29	4	Skeletal muscle	Oxidative muscles
Caramés[43]	2010	USA	C57BI/6J mice	9-12	4	Cartilage	_
Caramés[44]	2015	USA	GFP-LC3 transgenic C57BL/6J mice	28	5	Cartilage	_
Caccamo[45]	2013	USA	Tuberous sclerosis 2 heterozygous mice and Tau P301S transgenic mice	21	6 to 7	Brain	Microencapsulated rapamycin at a concentration of 14.8 ng/mg
Boyle[46]	2010	USA	Male C57BL/6J	18	3 to 6	Heart	_
Sun[47]	2018	China	Male diabetes mice with high fatdiet	8	6	Heart and artery	700 mg/kg by oral gavage purple sweet, potato color
Abhishek Kumar Singh[48]	2016	India-USA	Adult male Wistar rat model of Alzheimer's disease	–	4	Brain	Intra-hippocampal injection of amyloid-beta (Aβ1-42)
Sakuma[49]	2016	Japan	C57BL/6J mice	24	10	Skeletal muscle	_
Sacitharan[50]	2018	UK	C57BL/6 mice	16	3	Arthritic cartilage tissue	_
Rodríguez-Muela[51]	2013	Spain	C57BL/6 mice	12 And 22	6	Retina	_
Stranks[52]	2015	UK-USA	C57BL/6 mice	_	3	Macrophage	_

Table 1. Continued

First author	Publication year	Country	Species and Sex	Age (mon)	N	Tissue	Intervention/drug, dose range (mg/kg)
Rizza[53]	2018	Denmark-Italy	C57BL/6 Mice deficient in GSNOR (Gsnor−/−)	1-12	3 to 5	Brain & liver	_
Del Roso[54]	2003	Italy	Male Sprague Dawley rats	1-2-6-12-18-24	_	Liver macroautophagy	3,5-Dimethylpyrazole (12 mg/kg BW) intraperitoneally
Takahashi[55]	2017	Japan-USA	Fischer 344 × Brown Norway inbred rats	34	20	Muscle	1 mL/day of epigallocatechin-3-gallate (50 mg/kg BW)
Patricia Sosa[56]	2018	Spain	C57BL6 mice	24	10	Muscle	_
Chunfang Yi[57]	2018	China	Sprague-Dawley rats	4-6	5	Hippocampal neurons	4 mg/kg dexmedetomidine, I.P.
Zhang[58]	2015	China	Atg7-Floxed mice and Tyr::Cre mice, genetic deficiency	_	3 to 4	Melanocyte	_
Tang [59]	2018	USA	Wild-Type and Nrf2 Knockout (- / -) WT C57BL/6J mice	4- 12	5 to 6	Cerebral cortical tissue	_
Hao Xiong [60]	2019	China	Mir-34a+/- mice and SIRT1 transgenic (Tg) mice on the C57BL/6	3- 12	4 to 8	Cochlear hair cells in ear	7.5 or 300 mg/kg/day resveratrol, orally
Wohlgemuth SE[61]	2010	Italy-USA	Male Fischer 344 rats	6- 24	12 to 20	Skeletal muscle	8-10% calorie restricted, wheel running
Yeo[62]	2019	USA-Korea-Spain	Female C57BL/6J mice	2-24	7 to 14	Skeletal muscle	GFP-tagged PGC-1α (2.7 μg/mL)
Shuyi Wang[63]	2019	Spain	Akt2-AMPK double Knockout C57BL/6J mice	4-12	5 to 12	Myocardial tissue	DNA transfection
Gang Zhen[64]	2019	China	Male Sprague-Dawley rat	8	6 to10	Intervertebral disc degeneration	Tert-butyl hydro-peroxide: 30 mm
Dun-Sheng Yang[65]	2008	USA	Mutant human presenilin 1 and mutant amyloid Precursor protein (APP) transgenic PS/APP Mice	6, 16, 21-26	4 to 5	Brain	_
Wang[66]	2009	USA	Female C57BL/6 mice	4 and 24,28	5	Retina	_
Xue[67]	2016	China	Male Sprague-Dawley rat	3	3	Chondrocyte	Dexamethasone 25 μg/mL
Tonga[68]	2010	USA	LRRK2 Knock out in C57BL/6J (B6) mice	20	4	Brain	LRRK2 Knockdown
Wang[69]	2014	China	Male Sprague Dawley rats	2 , 6 , 12 and 20-24	5	Pancreatic tissue	_
Zhang[70]	2016	China	Male Sprague Dawley rats	2	3	Bone marrow	Cholesterol at 5, 10, Or 15 μg/mL
Zhang[71]	2010	China	C57BL/6 mice	8 and 24	8	Corpus cavernosum smooth muscle cells	Tankyrase 1 transfection
Wang[72]	2018	USA-China	C57BL/6 mice	4–6 and 24–26	6 to 9	Cardiac tissue	_
Xu[73]	2018	China	Male Sprague Dawley rats	3, 9 and 22	6 to 8	Liver	_
Zhu-Fei Guan[74]	2016	China	Male C57BL/6 mice	4	5	Brain	45 mg/kg streptozocin, I.P.
Zhang[75]	2017	USA-China	Male Sprague-Dawley rats and Institute of Cancer Research (ICR) mice	1.5-2	3	Liver	Dihydroartemisinin 3.5, 7, 14 mg/kg,
Yang[76]	2018	China	Male C57BL/6 mice/ male L2G85 reporter transgenic mice	3-3.5 /12-14 27-29	5	Cardiac tissue	_
Xu[77]	2017	China	Male Sprague-Dawley rats	_	3	Vascular smooth muscle cells	Celastrol 50, 100 nm
Wang[78]	2016	China	SAMP8	_	6	Brain	Rapamycin (0.5 mm)
Zhao[79]	2014	China	Sprague–Dawley male rats	5 and 25	5	Muscle, heart, kidney and liver	_
Wang[80]	2017	China	Female C57BL/6 mice, Nrip1 Global Knockout Strain (RY-Nrip1 KO), MP-Nrip1 KO mice	6, 12, 18, and 22	5	White adipose tissue	_
Guan[81]	2018	China	Male Db/Db−/− C57BL/6 mice	2, 8	5	Brain	Egb761 (50 mg/kg or 100 mg/kg) orally
Li[82]	2018	China	Heart-Specific SIRT3 KO (SIRT3-/-) Weaned C57BL/6 mice	4 and 20	8	Intervertebral disc	SIRT3-/-, aerobic intermittent training
Wu[83]	2019	China	Male Sprague-Dawley rats	20 to 22	6	Cardiac tissue	4 mg/kg of co-releasing molecules
Yamamoto[84]	2016	Japan	Atg5F/F-NDRG1 mice	2 and 24	4 to 5	Kidney	_
Zha[85]	2017	China	Sprague- Dawley rats	1-3 days neonatal	3	Cardiomyocytes	Ages (100 mg/mL),
Xu[86]	2016	USA-China	C57BL/6 Mice, MIF Knockout (MIF−/−) Mice	4-24	3 to 4	Cardiac tissue	_
Toshima[87]	2014	Japan	Atg5-deficient mice (L-Atg5 KO mice)	_	_	Liver	Partial hepatectomy
Xia[88]	2019	China	Male C57BL/6 mice	10	_	Retina	Blue light damage
Yan[89]	2018	China	Male, Sprague-Dawley, specific-pathogen-free rat	18	6	Brain	Intracerebroventricular injection of Raav-Ampkα1 (2 × 1012 mg/kg),
Yang[90]	2014	China	Male C57BL/6 mice	3, 12, and 20	4	Brain	Caloric restriction

SAMP8, senescence-accelerated mouse prone 8.

in these studies, whether the transgenic technology application for aging induction plays a dominant role or not, and subsequently what percent of studies used transgenic animals in this field, which markers of autophagy and aging were used frequently, and finally in which organs autophagy exerted the protective or detrimental role during the aging process.

Results

Upon the comprehensive search strategy, 80 articles identified regarding in vivo studies of autophagy effects in development of aging in different tissues. Through primary search in various data base (Ovid, PubMed, Embase, Scopus, ProQuest, and Web of Science) 9478 articles were found. Following duplicate removing (5465 articles) and screening of 4013 articles based on title and abstract, 3818 of records were exclude due to different reasons including: non-English published articles, in vitro experiments, clinical studies and abstracts presented at congresses. According to the assessment of full-text articles for eligibility inclusion, 115 full-text articles were excluded. Ultimately, 80 full-text of eligible studies were included in our qualitative analysis (Figure 1).

Based on our analysis, China and the US are two pioneer countries in the field of autophagy and aging correlation with 43.75 and 17.50 percentage, respectively. In this line, Spain and Japan are countries where 7.50% and 3.75% of works have been conducted in this field (Figure 2A). As shown in Figure 2B, it seems that autophagy and aging correlation is considered an interesting issue, which has drawn many researchers' attention in recent years, particularly in 2018 (26.25%).

Although most of the studies used male animals, there are no considerable differences regarding the obtained results between female and male animals. According to the extracted data, authors mostly defined aged animals in an extended range of 9-29 months to study aging in different tissues. Notably, according to our analysis, 31.25% of all animals had undergone genetic manipulations. In better words, some studies by using gene silence techniques (e.g., senescence-accelerated mouse prone 8 - SAMP8), as well as silencing or knocking out of the essential autophagic genes such as *Atg5* and *Atg7*, led to the aging induction to perform further experimental assessments (Figure 3A). However, there are no differences between aged and transgenic animals. Given that aging development is critical to promote various tissues dysfunction, making the body more susceptible to multiple diseases, we intended to study all tissues examined under the aging process. Based on our findings, brain tissue (27.50%), cardiovascular system (15.00%), and skeletal muscle (13.75%) are three main organs, which have received much attention in comparison with other tissues (Figure 3B). In addition, to determine whether autophagy is impressed during the aging process or not, we also explored the alternation of autophagy and aging-related-markers to find any reciprocal correlation between autophagy and aging.

As shown in Figure 4A, among selective proteins representing autophagy proceeding, LC3II (92.50%), P62 (63.8%), Beclin-1 (51.30), and different *Atg* genes (3, 5, 7, 12, and 14) (28.80%) have been studied more than the other markers (Figure 4A). Regarding aging specific markers, p proteins (16, 21, 27, 53, 57, and 66) have been used more frequently than other markers (23.8%). Moreover, other known markers, including senescence-associated beta-galactosidase (SA β-galactosidase), different apoptotic markers (NFκB, Bax, Bcl2, caspase 3, 7), and fibrosis/collagen deposition were used 21.30%, 16.30%, and 10.0%, respectively (Figure 4B).

Next, we evaluated the role of autophagy during the aging process in different tissues in all included articles. According to our results, autophagy exerts both protective

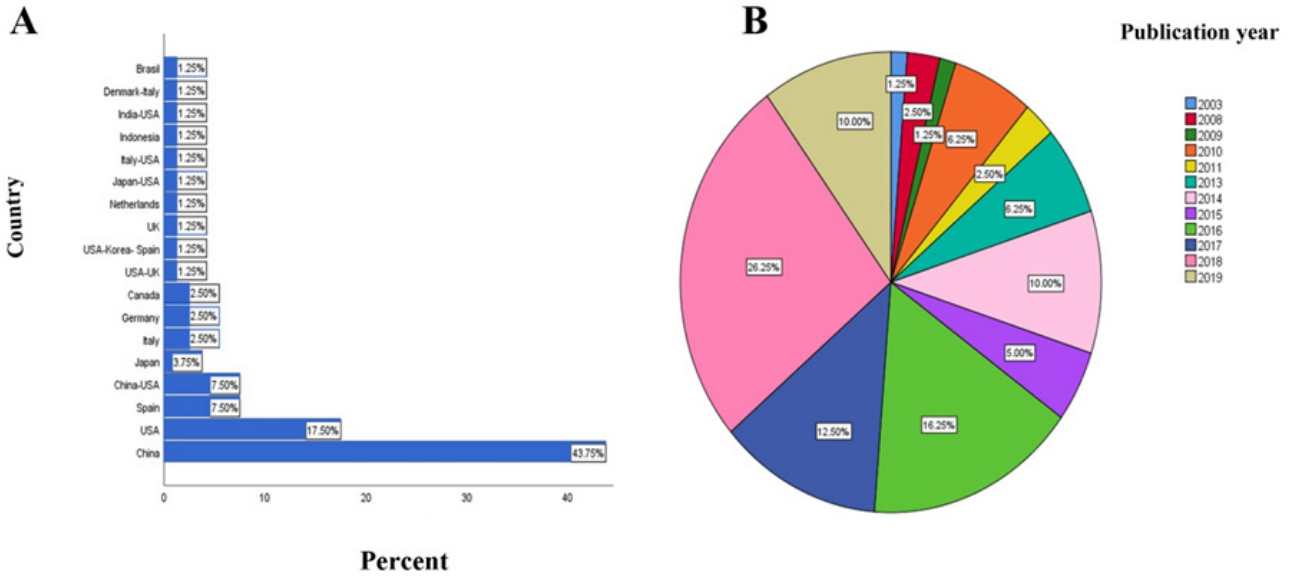

Figure 2. Statistical analysis regarding the included studies. (A) The percentage of all countrises participated in aging and autophagy relationship in animal models. (B) The percentage of studies in different years that have been conducted in the field of aging and autophagy.

and detrimental effects on divergent tissues through aging. However, in all studied articles on smooth muscle, bone/cartilage/chondrocyte, and adipose tissues, autophagy flux decreased during aging, suggesting the protective role of autophagy during aging. In other tissues, there are controversial results in which autophagy reduction during aging was higher than autophagy enhancement, further declaring the protective role of autophagy in this regard (Figure 5).

Despite abundant studies in this field, the exact role of autophagy during aging has not been completely deciphered. However, plausible mechanisms of action following the application of various drugs/chemical agents have been proposed in some studies. In Table 2, all probable mechanisms of action involved in autophagy modulation during the aging process are listed.

Discussion

To our knowledge, the aging is a physiological process that makes our body susceptible to various diseases and disabilities.[91] Currently, aging process is considered a critical issue, which has become interesting area for research. In present study, we systematically reviewed all animal studies in different aged tissues as well as the autophagy modulation under aging condition. According to the analysis of 80 studies, the most of the publications have been published in 2018 in China and the United States. Given that the brain, cardiovascular system and skeletal muscle tissue are likely affected during aging, the majority of studies were related to these tissues. In next step, the main markers of autophagy and aging were addressed. Based on statistical analysis, LC3, P62, Beclin-1, and multiple *Atgs* in autophagy and different classes of p proteins (p16 and p53), SA-β-gal, and fibrin/collagen deposition in aging were more prominent. One of the important outcomes in our study refers to the evaluation of autophagy alternation upon the aging onset, and to find whether autophagy exerts a protective or detrimental

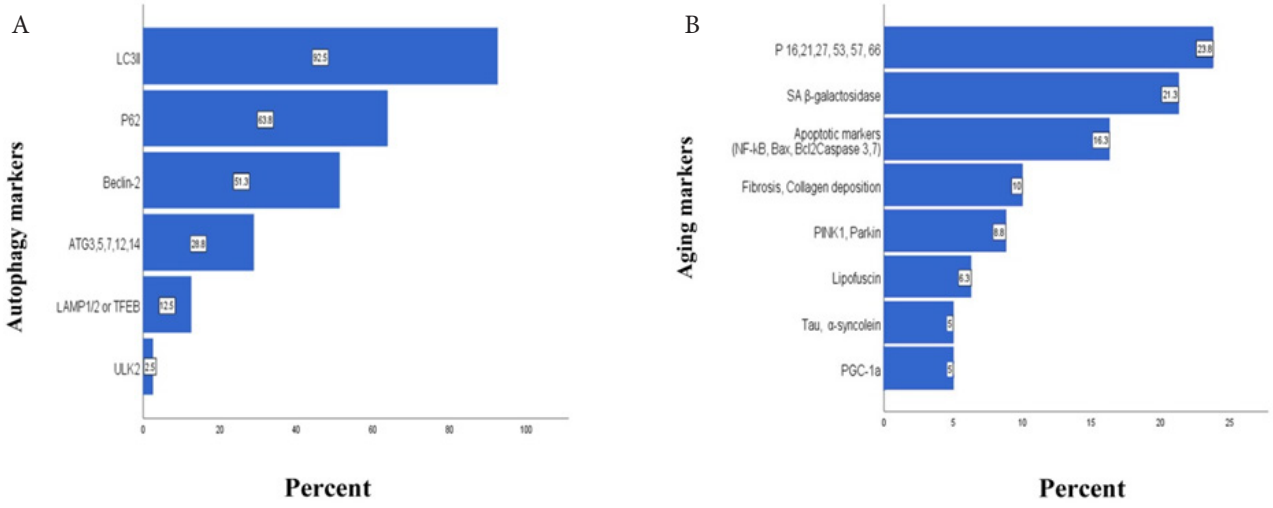

Figure 3. (A) The utilization of transgenic animals rateassessment (%). **(B)** ThePercentage of All Studied Tissues .

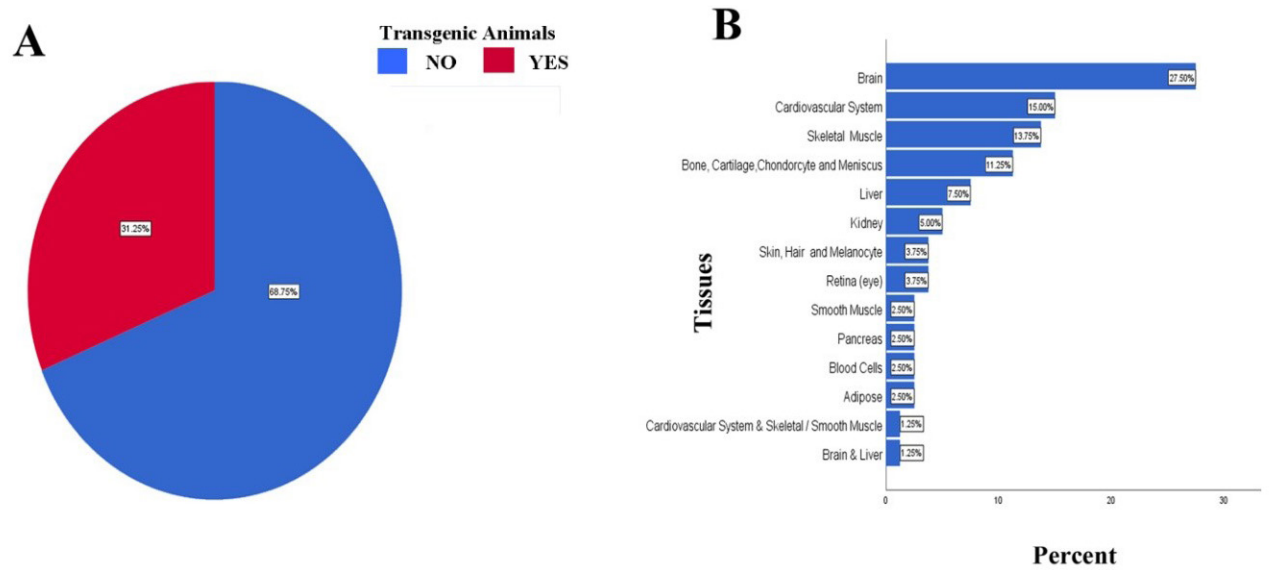

Figure 4. The percentage of important markers regarding autophagy and aging collaboration. (A) autophagy related markers (%). (B) Aging related markers (%).

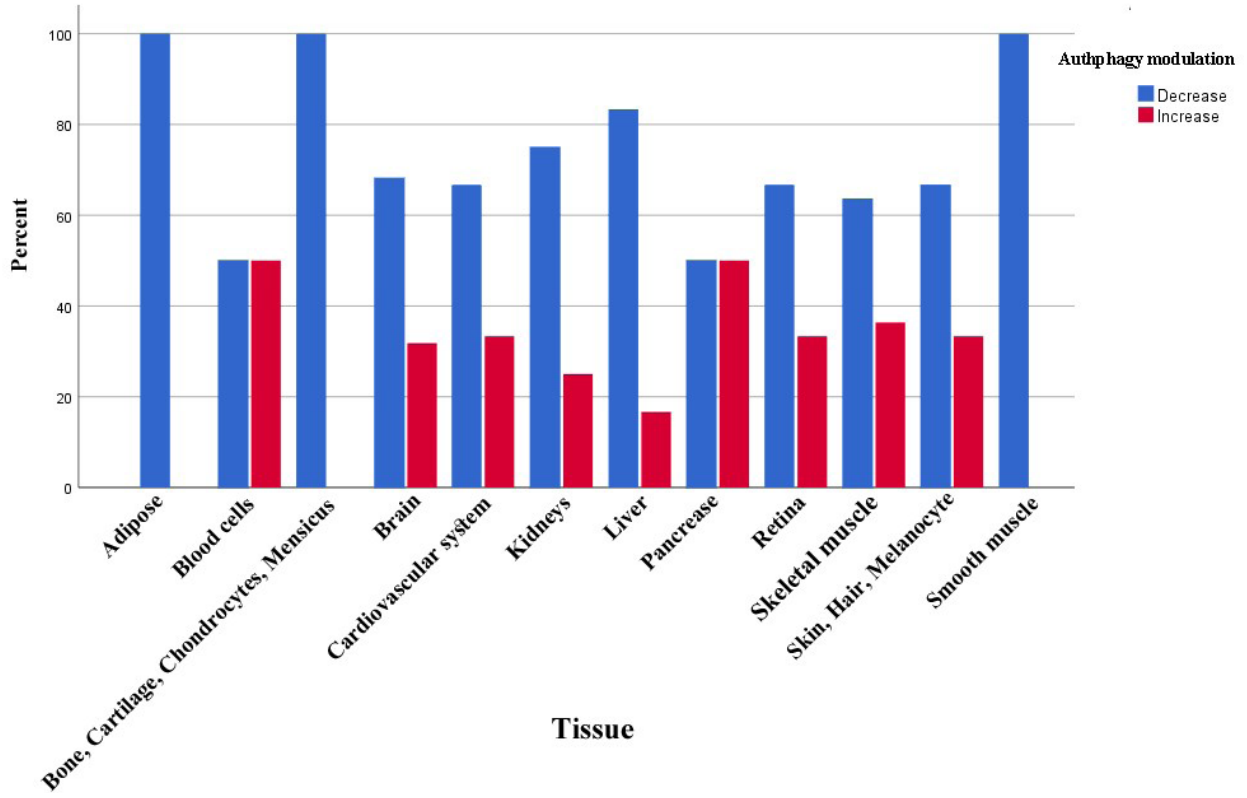

Figure 5. The representative alternation of autophagy activity during aging in different tissues.

Table 2. Different mechanisms of action involved in autophagy modulation

Drug/Chemical agents	Mechanism of action to modulate autophagy
Caloric restriction	*Short-term:* Inhibition of p-mTOR-ser2448, pS6K1-thr389, and p4E-BP1-ser65, Activation of SIRT1 and AMPK, *Long-term:* Oxidative damage and apoptosis regulation
Resistance exercise training	Apoptosis reduction, Modulating IGF-1, Akt/mTOR and Akt/FOXO3a signaling
Raav-AMPKα1	AMPK-Sirt1 signaling pathway
Blue light	• Increase of autophagy, • Mitogen-activated protein kinases (MAPK p38), • Protein kinase R-like endoplasmic reticulum kinase (PERK)
Carbon monoxide-releasing molecule-3	• Reversing mitochondrial membrane potential depolarization • Preventing cytochrome C release • Inducing mitochondrial accumulation of PINK1 (PTEN-induced putative kinase 1) and Parkin
Egb761	By regulation of beclin-1, LC3, and NF-κB
Rapamycin	• PI3K/Akt1/mTOR/EB Signaling, • ROS and p53 pathways
Celastrol	• Reducing ROS production, • Activation of autophagy
Dihydroartemisinin	GATA 6 accumulation
Streptozocin	Beclin-1- mediated autophagy
Tankyrase 1 transfection	mTOR signaling pathway
Cholesterol	Autophagy and ROS/p53/p21Cip1/Waf1 Pathway
Dexamethasone	mTOR signaling pathway
Tert-butyl hydro-peroxide	ROS induction
GFP-tagged PGC-1α	Mitophagic pathway and mitochondrial quality + ROS reduction
Resveratrol	miR-34a/SIRT1 signaling
Dexmedetomidine	Beclin-1-dependent autophagy-activated pathway
Epigallocatechin-3-gallate	Reduction of apoptotic signaling+ atrogene and mitochondrial associated stress signaling
Purple sweet potato color	Deactivation of the mTOR signaling pathway
Metformin	AMPK-dependent pathway
β-Asarone	Modulation of the ROCK signaling pathway
Caffeine	A2AR/SIRT3/AMPK pathway
RL-118, an 11β-HSD1 inhibitor	pAMPKα/AMPKα ratio and mTOR signaling pathway

effects on aged organs. Overall, it is worth to note that most of the included articles demonstrated that autophagy diminished significantly in aged tissues. Indeed, autophagy modulation induced by drug and chemical agents along with any genetic manipulation could be considered as a promising anti-aging therapy. We also addressed to the possible molecular mechanisms involved in the autophagy impacts. In this respect, one of the key signaling pathways is related to mammalian target of rapamycin (mTOR) signaling pathway. In fact, SIRT1/ AMP-activated protein kinase (AMPK)/mTOR axis is the master regulator of energy metabolism, playing an important role to modulate autophagy under different conditions such as aging.[92] In other words, this axis coordinates the majority of the responses to the energy status, particularly during aging when the regulation of its activity is impaired. AMPK, termed energy sensor, plays key role in regulating metabolism, cell growth, cellular senescence and autophagy.[93] Regarding autophagy process, AMPK and mTOR regulate autophagy through direct phosphorylation and activation of Ulk1/ BECN1.[93] Following aging, AMPK especially AMPK-α1 subunit activity and subsequently p-AMPK level decrease while mTOR/ p-mTOR increased. Sirtuin 1 (SIRT1), as a nicotinamide adenine dinucleotide (nad)+-dependent histone deacetylase, is a prominent regulator of deacylating proteins involved in multiple pathways of metabolism maintenance.[94] A previous study showed that SIRT1-dependent mitophagy has crucial role for cell adaptation under the hypoxic condition in aged organs.[95] Given that the anti-senescence impact of caffeine mediated by autophagy activation in skin, some molecular mechanisms are related to adenosine A2a receptor (A2AR) inhibition, SIRT3, and AMPK enhancement. Interestingly, sirtuin family especially SIRT1 and 3 have obtained more interests among researchers in aging field due to localization into the mitochondria.[96] To our knowledge, AMPK is a downstream target of SIRT3 that both of them are known positive regulator of autophagy/mitophagy in response to cellular senescence induced by ROS.[97] It has also been implicated that there is a fine-tuning reciprocal function between SIRT1 and AMPK during aging by mitophagy coordination.[98,99] Intriguingly, the anti-aging effect of some miRNAs also has been validated. For instant, resveratrol as a SIRT-1 activator exerted an anti-aging effect through miR-34a/ SIRT1 signaling pathway, oxidative stress reduction, and mitophagy coordination.[100] In fact, SIRT1 has a vital role to adjust balance between mitophagy and mitochondrial biogenesis.[101] Although plethora of disparate body of data declared that autophagy decreased over the course of aging, there are some controversial data explicated the autophagy elevation in parallel of cellular senescence. Within 80 studies, virtually 28 percentage inferred that autophagy related markers exerted an upward trend during aging. One reason to explain these conflict results could be related to the wrong data expression solely based on early-stage selective markers such as LC3 without consideration of last autophagy related degradation process. In better words, upon autophagolysosome blocking, the levels of LC3 could be falsely increased in spite of the ultimate inhibition of this process. To note, p62, as well-known ubiquitin-like autophagic substrate, decreased following the autophagic flux, which can be implicated the autophagy activation. However, it is worth mentioning that the long-term activation of the catabolic pathways like autophagy may switch from pro-survival strategy into a pro-aging mechanism (Figure 6).

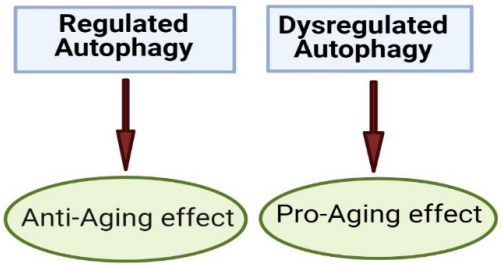

Figure 6. A schematic illustration of autophagy potential against the aging process.

Conclusion

Despite the controversial effects of autophagy, the majority of results indicated autophagy downregulated during aging. Therefore, it has been concluded that the regulated autophagy would be an anti-aging approach while excessive activity of autophagy promotes pro-aging processes.

Conflict of Interest

The authors declared that they have no conflicts of interest.

Ethics approval

Not Applicable.

Authors' contributions

FS and NV: articles selection; AR: Study designing and Writing the manuscript; HH: doing the statistical analysis.

Study Highlights

What is current knowledge?

- The plethora of disparate body of evidence declared that autophagy decreased over the course of aging,

What is new here?

- We postulated that autophagy activating agents could slow down the aging process,
- AMPK related signaling pathways play crucial role in anti-aging regulation,
- Overexpression or long-term activation of some catabolic pathways like autophagy may switch from pro-survival strategy into a pro-aging mechanism

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