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Autophagy in COPD

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ABSTRACT

Autophagy is an important cellular homeostatic process, where cell self-degrades long-lived proteins and damaged sub cellular organelles and proteins with the help of lysosomes in eukaryotic cells. In the past decade, remarkable advances have been made in describing autophagy as clinically relevant target to the treatment of pulmonary diseases. In this review I attempt to provide an overview of autophagy signaling pathway and also summarize the recent studies that suggest direct relevancy and function of autophagy pathway in the Chronic Obstructive Pulmonary Disease (COPD). However, further resolution of autophagic proteins and mechanisms is warranted in specifically designing autophagy-based therapeutic targets in COPD.

Keywords: *Autophagy, Oxidative stress, COPD, Cigarette smoke, Lung cancer*

INTRODUCTION

Mammalian macroautophagy (hereafter referred as autophagy) is evolutionary conserved degradative pathway that involves the fusion of double membrane autophagosomes and lysosomes for the turnover of free amino acids and fatty acids [1,2]. In addition to this, two other forms of autophagy mechanisms have been described. One type involves the invagination of lysosomal membrane to engulf cytosolic components into intralysosomal vesicles termed as microautophagy [3]. In chaperone-mediated autophagy, proteins with a particular consensus motif (KFERQ) are selectively delivered across the lysosomal membrane for degradation [4].

Autophagy can be upregulated in response to multiple forms of physiological stress including starvation [5], growth factor deprivation [6], reactive oxygen species [7], hypoxia [8], hyperoxia [9,10], endoplasmic reticulum stress [11], DNA damage [12], protein aggregates [13] or pathogens [14]. Therefore, autophagy can be predominantly viewed as a cellular response pathway to a variety of stress stimuli rather than a nutrient deprivation response pathway. Chronic or acute exposure of the aforementioned stimuli can result in dysregulated or deranged autophagy pathway with the development of several pathological conditions. In this regard stimulant cigarette smoke upon chronic exposure has recently demonstrated an increased expression of autophagy markers in the development of COPD [15,16]. A better understanding for the role of autophagy pathway in COPD will help support in the design of the therapies for the cure of COPD.

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THE SIGNALING PATHWAY OF AUTOPHAGY

The molecular machinery of autophagy is orchestrated by approximately 30 autophagy-related (atg) genes and sets into action with the (1) Initiation of isolation membrane or phagophore formation. Origin of phagophore requires molecular component Unc-51-like kinase (ULK) complex; (2) Elongation of phagophore requires Beclin1 / class III phosphatidylinositol 3-kinase (PI3K) complex. Atg9 and vacuole membrane protein 1 (VMP1) are two components essential for the translocation of LC3 to autophagosomes [17]. In addition, Atg9 and VMP1 provide lipids to the phagophore; (3) Maturation and fusion between autophagosome and lysosomes to form autolysosome. The fusion step requires Atg12, LC3, Rab7, ESCRT, SNAREs and Vps protein components (Fig. 1) [18-20].

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Autophagy in Chronic Obstructive Pulmonary Disease

COPD is a progressive heterogeneous pulmonary disease characterized by the presence of persistent airflow obstruction upon chronic exposure to particulate matter (i.e., cigarette smoke, asbestos etc.)[21,22]. COPD is the third leading cause of death in United States, as it accounted approximately 134000 deaths in the year 2009 alone. In the year 2030, COPD has been predicted to be the fourth ranked disease of burden worldwide [23,24]. COPD, the major and global health epidemic, is the most common disease out of all the cigarette smoking maladies. Although cigarette smoking is the primary causative agent for COPD, it is also seen in nonsmokers, predominantly in developing countries indicating the disease is multifactorial. In patients with COPD, lung cancer and cardiovascular disease are the most common causes of death [25].

With respect to the lung, COPD is comprised of two features, (1) airway obstruction (bronchitis) and (2) lung parenchyma obliteration (emphysema). For the first time, Choi and colleagues have demonstrated the association of autophagy markers in human lung tissue from patients with COPD. In parallel, increased expression of autophagic proteins have been described in mouse lung tissue subjected to chronic exposure of cigarette smoke [15,26]. These studies have triggered attention to the possible causative association between autophagy and COPD. In the clinical specimens of COPD patients, markers of autophagy were upregulated in the early stages of disease progression, while caspase activation was examined at the later stages of disease progression. This might indicate that autophagy is attempting to protect during the initial stages from cigarette smoke-induced stress [27]. However, autophagy might give up and can result in the activation of apoptosis. Other possibility might be that autophagy is predecessor of apoptosis in response to disease stress in the lung.

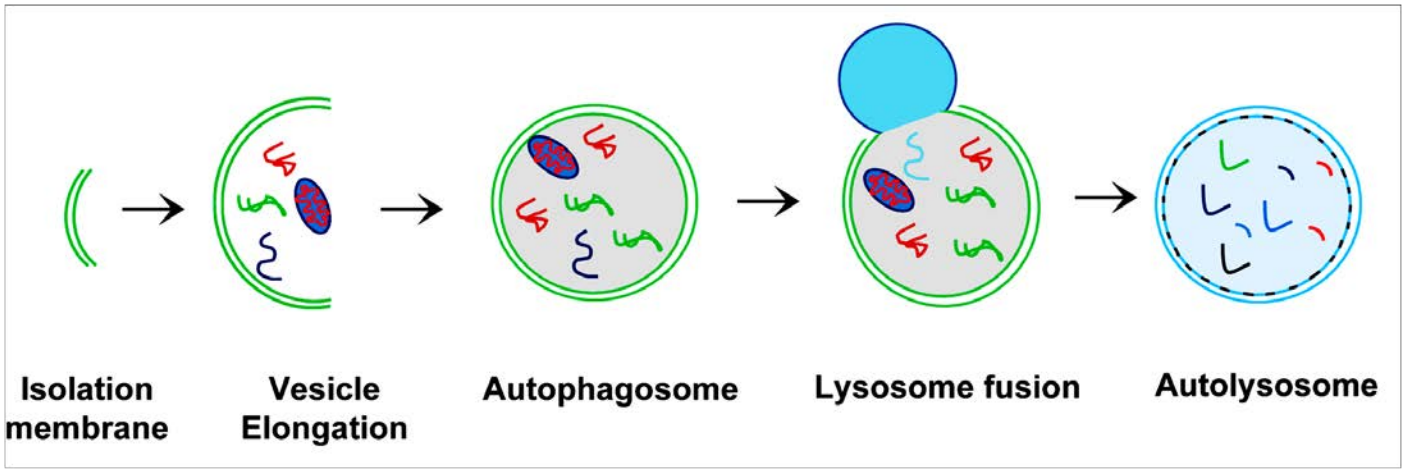
Using cultured lung epithelial cells and LC3B$^{-/-}$ mice systems, a functional role for autophagy pathway in cigarette smoke-induced emphysema have been identified. In an elegant study, Chen and co-workers demonstrated significantly decreased apoptotic indices and emphysema development in LC3B$^{-/-}$ mice exposed to cigarette smoke. These studies indicate autophagic pathway promotes apoptosis in response to cigarette smoke exposure. However, it remains unclear whether autophagic flux is involved in the epithelial cell death in COPD. Therefore, further resolution of autophagic proteins should be studied in detail to confirm the pro-apoptotic effects in COPD [28].

Little is known about transcription factors that regulate the transcription of autophagy genes. In this regard, transcription factor early growth response-1 (Egr-1) has been characterized as an immediate early response gene that is elevated after a variety of stress stimuli. Studies of cigarette smoke exposure revealed that Egr-/- mice were resistant to cigarette smoke-induced airspace enlargement indicating a potential role in lung development [27]. Of note, Egr-1$^{-/-}$ mice basally exhibited airspace enlargement, as compared to wild-type controls.

Oxidative Stress, Autophagy and Chronic Obstructive Pulmonary Disease

Oxidative stress and carbonyl stress are the two etiological factors that drive COPD both in heavy smokers and normal middle aged adults. In support of this, Schaberg and colleagues demonstrated activated heterogeneous alveolar macrophages and release of increased amounts of reactive oxygen species in COPD patients [29]. Oxidative stress generated from environmental and cigarette smoke causes tissue damage through oxidation of proteins, lipids, carbohydrates and DNA. Further, protein oxidation and protein carbonylation is a predominant driver and identified as underlying pathological phenotype associated with many chronic diseases [30]. Numerous studies suggest that oxidative stress regulates autophagy and serves as a link between these processes [31]. Therefore, targeting oxidative stress by modulating autophagy and by enhancing the endogenous antioxidant mechanisms specifically in proximal and distal lining of lung epithelial cells may prove to be beneficial in the treatment of COPD.

Figure 1: Schematic diagram representing the stages of autophagy pathway.



Conclusions and Future Perspectives

In summary, there are currently no treatments that slow the progression of COPD. Autophagy regulation can be noticed in lung bronchial and epithelial cells and macrophages upon exposure to cigarette smoke and in the patient lungs of COPD. Numerous studies both *in vitro* and *in vivo* suggest autophagy can be context specific in relation to cell death but may reveal its potential role and mechanistic link in the treatment and management of COPD. Further experimental studies are needed to determine the functional significance of autophagy in this heterogeneous disorder, COPD. In a larger context, further research including loss and gain of function studies, proteomics, genomics and metabolomics studies are needed that may unravel the novel detailed mechanisms and therapeutic targets for pulmonary diseases including COPD.

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Authors Column

I completed Doctorate degree in Cell and Molecular Biology from University of Strathclyde Glasgow, United Kingdom in the year 2010. During my PhD tenure, I developed an immense interest in autophagy, apoptosis, necrosis and ubiquitination fields. I was quite intrigued and came to understand the immense importance of autophagy and its involvement that encompasses a range of processes including normal development, maintenance of cellular and organismal health, ageing and to the pathogenesis of diverse diseases. After coming to Yale University in 2011, I work on the functional role of autophagy pathway in Hyperoxia-induced acute lung injury. My record of accomplished and productive research and technical knowledge in an area, which is highly relevant to autophagy, has led to write this review article.

