Mini Review

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2019.18.003182

Autophagy in Amiodarone induced Lung Fibrosis: A Close Look

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ARTICLE INFO

Received: May 27, 2019

Published: June 06, 2019

ABSTRACT

Citation: Poornima Mahavadi. Autophagy in Amiodarone induced Lung Fibrosis: A Close Look. Biomed J Sci & Tech Res 18(4)-2019. BJSTR. MS.ID.003182.

Autophagy

Autophagy is a fundamental lysosome-dependent cellular quality control mechanism [1]. The process involves orchestrated interactions of several autophagy related gene (atg) products that help in sequestration of cargo into characteristic double-membrane structures called autophagosomes [1,2]. Lipidated from of microtubule-associated proteins 1A/1B light chain 3B (MAP1LC3B/LC3B) marks the autophagosomes which then fuse with lysosomes to degrade their cargo. Autophagy primarily aims at cell survival but its deregulation results in the activation of several cell death pathways that play a pathomechanistic role in the development of several pathologies [3]. Such dysregulated autophagy has been indicated in the pathology of Diffuse Parenchymal Lung Diseases (DPLDs) [4-8], a group of lung pathologies that affect the pulmonary interstitium, alveolar epithelium and capillary endothelium [9].

Amiodarone

Amiodarone (AD) induced pulmonary fibrosis falls under the category of drug induced form of DPLDs [9]. AD is an antiarrhythmic drug and possesses typical class III Vaughan-Williams properties [10,11]. It is extremely effective in treating different kinds of arrhythmias but is a drug of last choice because of its contraindications. Pulmonary toxicity, especially confluent lung fibrosis is one of the severe side effects of amiodarone ultimately resulting in the death of patients. Patients receiving AD as low as 200 mg per day also develop severe pulmonary complications. Therefore, it is prescribed to treat atrial fibrillation strictly in the absence of pre-excitation and only when other agents become unsuccessful [12]. Characteristic Alveolar Epithelial Type II Cell (AECII) hyperplasia and foamy macrophages are typical cellular features of AD induced lung fibrosis. Additionally, AD results in AECII apoptosis in patients as well as in animals [13-15]. Appealing studies have shown that AD gets enriched in lysosomes and results in multilamellar body accumulation in several cell types [16,17]. Supporting this concept, we also showed that in response to AD, lamellar body membranes in AECII are closely connected with autophagosomal structures [8].

Role of Autophagy in AD Induced Lung Fibrosis

Both AD and its derivate dronedarone induce autophagy [18]. We and others have shown that AD promotes and increases autophagy flux and thereby apoptosis of alveolar epithelial cells in vitro. Supporting this, inhibition of autophagy firstly in vitro by LC3B gene silencing rescued Mouse Lung Epithelial Cells (MLE12) from AD induced apoptosis [8]. In addition and of note, an elegant study by Uhal & colleagues that focused on the role of angiotensin system antagonists in AD induced lung fibrosis showed that rats treated with AD followed by treatments with the angiotensin converting enzyme inhibitor captopril as well as the angiotensin receptor antagonist losartan significantly reduced AD induced alveolar epithelial cell apoptosis as well as alveolar wall collagen accumulation [19]. It is noteworthy that both these drugs are reported to inhibit autophagy [20,21]. Although not directly proved, it may be speculated that the attenuation of AD induced alveolar epithelial cell apoptosis and thereby lung fibrosis by these drugs may at least in part act via autophagy inhibition.

On the other hand, Transcription Factor EB (TFEB), known as a master gene for lysosomal biogenesis is activated and translocated to the nucleus upon AD treatment. Further data indicated that

the overexpression of TFEB proved to be protective towards AD induced phospholipid accumulation [22]. One intriguing study by Lee& colleagues showed cell and dose specific effects of AD on autophagy. A further activation of autophagy by rapamycin rescued AD induced goblet cell hyperplasia, airway inflammation, and mucin secretion in rats.

Conclusion

It is now well-documented that AD induces exaggerated autophagy, alveolar epithelial cell stress and apoptosis and subsequent lung fibrosis. It may be alluring to take the next steps towards therapeutic targeting of this pathway but in view of the multifaceted functions of autophagy, a concrete understanding of the mechanisms behind dysregulated autophagy in AD induced lung fibrosis are still warranted to design therapeutic interventions that fine tune the autophagy pathway in this disease.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2019.18.003182

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