Autophagy is deficient in nasal polyps: Implications for the pathogenesis of the disease

Ling-Feng Wang, MD,1,2 Jeff Yi-Fu Chen, PhD3, Chen-Yu Chien, MD1,4
1Department of Otolaryngology, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
2Department of Otolaryngology, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan
3Department of Biochemistry, Kaohsiung Medical University, Kaohsiung, Taiwan
4Department of Otolaryngology, Kaohsiung Municipal Hsiao Kang Hospital, Kaohsiung, Taiwan

Abstract

Purpose: Autophagy has been implicated in many chronic inflammatory diseases including chronic airway inflammation. We will investigate the role of autophagy in the pathogenesis of nasal polyp.

Methods: We studied LC3 protein expression, a common indicator of autophagy, in fresh tissue specimens of five nasal polyps and five control nasal mucosa by Western blot analysis. The results were also confirmed by immunohistochemistry (IHC) using additional twenty-five paraffin-embedded nasal tissue sections. Finally, the autophagic activity was validated in nasal polyp-derived fibroblasts by evaluating the number of green fluorescent protein (GFP) labeled LC3 puncta.

Results: The expression of LC3 was dramatically decreased in all five nasal polyp tissues. In contrast, Akt-mTOR signaling, an established negative regulator of autophagy, was significaantly activated in these tissues. Immunohistochemical results further demonstrated a negative correlation between autophagy and nasal polyps (P < 0.05). GFP-LC3 puncta formation, an alternative indicator of autophagy, was also diminished in nasal polyp-derived fibroblasts (P > 0.01).

Conclusion: Autophagy is deficient presumably due to suppression by high Akt-mTOR signaling activity in nasal polyps, which has offered novel insights into the mechanism and therapeutics of the disease.

Introduction

Chronic rhinosinusitis with nasal polyps (CRSsNP) are histologically characterized by increased inflammatory cell infiltration. Various exogenous agents including virus, bacteria, fungi and allergens have been hypothesized to be the etiological factors. However, the initiating event that triggers abnormal and persistent inflammation in CRSsNP remains unidentified.

Autophagy is a cellular process that delivers cytoplasmic components to lysosomal degradation for protein and organelle turnover, which is essential for diverse physiological functions such as survival, differentiation, development and homestasis. However, the role of autophagy in NP pathogenesis is yet to be defined.

The aim of this study was to investigate the expression of autophagy in NPs and control nasal mucosa. We speculated that the autophagic level was drastically reduced in NP tissues and NP-derived fibroblasts possibly due to the activation of Akt-mTOR signaling pathway.

Inhibition of Autophagy in Nasal Polyp Tissues

As shown in Figure 1, Akt and mTOR, the known negative regulators of autophagy, were highly activated in almost all five NP cases, as the phosphorylation levels of Akt (p-Akt) and mTOR (p-mTOR) were significantly elevated in NP tissues compared to those in control mucosa. In sharp contrast, LC3-II expression, the common indicator of autophagic activity, was nearly vanished in the five NP cases, exhibiting an inverse correlation with the activity of Akt and mTOR.

IHC Staining for Autophagy Markers and the Correlation with Nasal Polyps

In control mucosa, LC3-IHC was primarily present in the cytoplasm of inflammatory leukocytes and stromal cells in submucosa. On the other hand, p-mTOR IHC in NP tissues was localized primarily in the cytoplasm of the epithelium (Figure 2). In contrast to control mucosa, the majority of NP tissues (10/12) had negative or weak LC3 staining intensity (P < 0.025). Conversely, most of the NP tissues (10/12) but only NNM (0/1) showed moderate to strong p-mTOR staining intensity (P < 0.001) (Figure 2 and Table).

Reduced Autophagosome Formation in Nasal Polyp-Derived Fibroblasts

The number of puncta per cell in NP-derived fibroblasts was significantly lower than that in control mucosa-derived fibroblasts (P < 0.01) (Figure 3), suggesting reduced autophagic activity in NP-derived fibroblasts.

Discussion

In this study, we showed that autophagy was largely suppressed in NPs presumably due to the highly activated Akt-mTOR signaling pathway. Currently how mechanistically autophagy deficiency may affect NP pathogenesis is unknown. Several human inflammatory diseases have been associated with autophagy. More interestingly, there are previous studies indicating an inverse correlation between autophagy and inflammation in different cell contexts, raising the possibility that autophagy might impact nasal polyposis through modulating inflammatory responses.

Conclusions

In summary, to our knowledge, this study has demonstrated the first implication that autophagy could be involved in the molecular mechanism of NP pathogenesis. Further study is needed to investigate its possible mechanism.

References


Contact

Ling-Feng Wang, MD
Department of Otolaryngology Head and Neck Surgery, Kaohsiung Medical University
Email: lifwang@kmu.edu.tw
886-7-3121155-5009