Brief Report

The role of autophagy-related gene 9B in lichen planus

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Abstract

Background: Lichen planus (LP) is an idiopathic, chronic, relapsing, inflammatory, autoimmune dermatological disease. The etiopathogenesis of LP is still unclear. Autophagy is a strictly regulated lysosomal degradation pathway that is crucial for maintaining intracellular homeostasis and normal development. The dysregulation of autophagy-associated genes was recognized to increase the susceptibility to multiple diseases, including inflammation, autoimmune disorders and cancer.

Aims: Our study aimed to detect the expression of autophagy-related gene 9 b (ATG9B) in LP patients compared to normal control persons to investigate the possible role of autophagy in pathogenesis of this disease.

Methods: This case–control study included 30 LP patients and 30 age-, gender-matched healthy controls. Four millimeters punch skin biopsies were obtained from LP lesions and from the controls and they were kept in lysis solution for the stability of the studied parameters and were kept frozen at –80°C till analysis of ATG9B using real-time polymerase chain reaction.

Results: The level of ATG9B in lesional skin of LP was significantly decreased compared to normal control persons ($P < 0.01$); also, there was a non-significant relation between ATG9B level and age, sex, duration and family history among LP patients.

Limitations: Limited number of patients included in our study (30 patients).

Conclusion: Autophagy may play a role in the pathogenesis of cutaneous LP.

Key words: Autophagy, autophagy-related gene 9 b, lichen planus

Introduction

LP is a chronic idiopathic relapsing inflammatory papulosquamous and presumably autoimmune disease that affects the skin, mucous membranes, nails and hair.

The cause of LP is unknown and has no involvement of any known pathogen. T-cell-mediated autoimmune reaction may be involved in pathogenesis of the disease. This autoimmune process triggers apoptosis of the epithelial cells. Several cytokines are included in LP pathogenesis, including tumor necrosis factor alpha, interferon gamma, interleukin-1 alpha, interleukin 6 and interleukin 8.[1]

Autophagy is a process that is present in all cells at low levels under normal conditions, but many stimuli such as hypoxia or starvation may lead to its upregulation. Cytoplasmic components are broken down into basic components and returned to be reused in the cytosol.[2]

Autophagy is mediated by an organelle called autophagosome. As autophagosomes engulf a part of cytoplasm, the autophagy is generally thought to be a non-selective degradation system.[3]

Besides mediating survival and homeostasis of the cells, autophagy is important in the antigen processing and

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presentation and in secretion of pro-inflammatory cytokines such as type I-interferon and tumor necrosis factor-α.[2]

ATG9B is the integral transmembrane protein among autophagy-related gene proteins in the core that is required for the autophagosome formation. The importance of it includes the autophagy regulation and innates immune signaling inhibition.[2]

The aim of our study was to evaluate the role of autophagy in pathogenesis of LP through the evaluation of ATG9B expression in tissue biopsies from normal and LP skin.

Methods

Thirty (30) patients with lichen planus and thirty (30) healthy controls were enrolled in the study. All patients and healthy controls recruited from individuals attending the outpatient clinic of Beni-Suef University Hospitals, Egypt, in the period (from December 2017 to May 2018).

Exclusion criteria included the use of any topical or systemic treatment for LP in the past three months, patients with associated systemic, dermatological or other autoimmune disease.

Patient information was collected by single dermatologist (RMN) including age, sex, family history, clinical types of LP and duration of the disease.

The aim of our study was explained to each patient, and an informed consent was taken from each of them. The protocol of the study conforms to ethical guidelines of the 1975 Declaration of Helsinki as reflected in the a priori approval by Institution Human Research Committee.

The estimation of ATG9B in the tissue was performed using the quantitative reverse transcripton PCR (qRT PCR).

Statistical analysis

Data had been coded and entered using Statistical Package for the Social Sciences version 22. Data had been summarized using mean, standard deviation in the quantitative data and using frequency (count) and relative frequency (percentage) for the categorical data. Suitable statistical tests were used (Chi-square, one-way ANOVA, one sample *t*-test and Pearson's and Spearman's correlation) whenever needed. $P < 0.05$ was considered statistically significant.

Results

The gender ratio and age were not substantially different for each variable among patients with LP (20 men and ten women; mean ± SD age [38.9 ± 13.6]) and healthy controls (16 men and 14 women, mean ± SD age [27.9 ± 7.1]). Clinical data of participants are presented in [Table 1]. *P*-value for age is 0.55 and *P*-value for sex is 0.196.

The tissue ATG9B expression

The expression level of ATG9B in LP cases ranged from 0.1 to 0.8 with mean value of 0.3 ± 0.2 and that was significantly lower than in controls which ranged from 0.98 to 1.30 with mean value 1 ± 0.1 and $P < 0.01$ [Table 2].

We found no relation between patient age, sex, disease duration and family history with ATG9B expression [Table 3].

Discussion

The pathogenesis of LP appears to be complex with interactions among genetic, environmental and lifestyle factors, LP is probably a multifactorial disease, sometimes induced by drugs, may be with liver disease, often idiopathic and with an immunopathogenesis involving T-cells in particular.[4] Clinical variants of LP include actinic, follicular, mucosal, atrophic, hypertrophic, LP pigmentosa and LP pemphigoides. Corticosteroid cream or ointment may be used if LP is localized and systemic steroids are preferred

Table 1: Demographic data and clinical characteristics of the LP patients and controls

Items	Patients (*n*=30), *n* (%)	Controls (*n*=30), *n* (%)
Gender, *n* (%)		
Males	20 (66.7)	16 (53.3)
Females	10 (33.3)	14 (46.7)
Age (years), mean±SD	38.9±13.6	27.9±7.1
Duration of LP (months), mean±SD	10.5±10.9	
LP types, *n* (%)		
Eruptive	4 (13.3)	
Classic	15 (50.0)	
Hypertrophic	6 (20.0)	
Nail	2 (6.7)	
Oral	2 (6.7)	
Actinic	1 (3.3)	
Family history of LP (%)		
Negative	90.0	100
Positive	10.0	0

LP: Lichen planus, SD: Standard deviation

Table 2: Comparison of the expression level of ATG9B between cases and controls ATG9B

	ATG9B					
	Mean	SD	Median	Minimum	Maximum	*P*-value
Cases	0.32	0.19	0.24	0.11	0.83	*<0.01*
Controls	1.03	0.07	1.00	0.98	1.30	

ATG9B: Autophagy-related gene 9 b

Table 3: Correlation analysis between ATG9B and age, sex, duration and family history among lichen planus patients

Items	ATG9B (median)	*P*-value
Age in years	0.24	0.837
Sex	0.20	0.131
Duration of LP	0.108	0.606
Family history	0.21	0.948

ATG9B: Autophagy-related gene 9 b

in severe cases. Immune response modifiers could be of value in severe signs and symptoms of the disease such as azathioprine, mycophenolate, cyclosporine and methotrexate. Antihistamines may relieve the itching of LP. Phototherapy might clear up LP affecting the skin. Retinoids are used if there is no response to corticosteroids or phototherapy.[5]

Autophagy is a regulated lysosomal degradation process which is essential for maintaining the intracellular homeostasis and also normal development.[3] Autophagy is included in multiple innate and adaptive immune processes, such as pathogen recognition and destruction, antigen processing for major histocompatibility complex presentation, regulation of lymphocyte development, function and inflammation. After being stimulated by T-cell receptor activation on antigen recognition, autophagy can be induced in T cells and is required for T-cell proliferation, differentiation, survival and death. Autophagy is important trafficking event in mediating T-cell response and regulating T-cell immunity. Thus, T-cell autophagy is hypothesized to be involved in LP pathogenesis.[3]

Defects in autophagy-related genes and recruitment of autophagy proteins are important for autophagic dysfunction. The defect in regulation of autophagy-related genes was recognized to increase susceptibility to different diseases, such as inflammation, autoimmune skin diseases such as vitiligo and cancer.[6]

All the above-mentioned findings prompted us to investigate the possible role of autophagy in LP and to do so, we estimated ATG9B level in tissue.

We reported that the expression level of ATG9B in LP cases ranged from 0.1 to 0.8 with mean value of 0.3 and that was significantly lower than in the control group. The functions of ATG9B include the regulation of autophagy and inhibition of the innate immune signaling. Decreased expression of the gene may lead to autophagy dysregulation in T cells of LP lesions.[2]

Limitation

Limited number of patients included in our study (30 patients), so additional studies on large number of cases are needed to determine its exact role in pathogenesis of LP.

Conclusion

Autophagy may play an important role in the pathogenesis of cutaneous LP, particularly through ATG9B, it can be used as a biomarker to evaluate its progression and effect of therapeutic interventions.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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