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Research Article

Expression of Apoptosis Activating and Cell Proliferation Proteins in Oral Lichen Planus

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A B S T R A C T

Aims and Objectives: Oral lichen planus is an immune-mediated mucocutaneous disease of unknown etiology characterized by the destruction of keratinocytes via apoptosis by infiltrating T lymphocytes. Though cytotoxic T lymphocytes can activate both extrinsic and intrinsic pathways of apoptosis, key proteins involved in both pathways have not been studied or there are conflicting results in english literature. The aim of the present paper was to study the key proteins involved in extrinsic & intrinsic pathways of apoptosis as well as products of genes involved in cell proliferation in cases of oral lichen planus.

Material and Methods: The study was undertaken at Maulana Azad Medical College New Delhi. Thirty histopathologically confirmed cases of oral lichen planus were included in this study. The presence of apoptosis was identified by TdT-mediated dUTP-biotin nick-end labelling. The expression of caspase-3, caspase-8, caspase-9, bax, K-ras, c-jun and c-erb-2 was studied by immunohistochemistry on histopathology sections.

Results: A statistically significant increase in all the proteins studied and apoptosis was found as compared to the control subjects. The association between apoptosis: caspase-3, caspase-3: capase-8, caspase-9: bax, caspase-8: caspase-9 and caspase-3: caspase-9 was also significant. An inverse association was found between c-jun: apoptosis, c-erb-2: apoptosis.

Conclusion: We found increased expression of proteins involved in both the pathways of apoptosis as well those associated with cell proliferation. Our results suggest that apoptosis is occurring via both pathways in oral lichen planus. There is also increased cell proliferation which may be responsible for the later development of malignancy in cases of oral lichen planus.

Keywords: Lichen, Apoptosis, Cytotoxic T-cells, Disease

Introduction

Lichen planus is a mucocutanous disease, first described by Erasmus Wilson in 1869.[1] The prevalence of lichen planus ranges from 0.1%-2.2% worldwide.[2,8] In the urban areas of India, the prevalence of oral lichen planus range from 0.02%-0.4%, while in villages it varies from 0.1%-1.5%.[9,13]

The lichen planus is a disease of the middle-aged and elderly with most cases occurring from 30-70 years.[14,16] However it has also been reported in infants under the age of six months.[17,18] Bhattachrya et al. have reported the age range of 8-76 years in the Indian population.[9]

Its premalignant nature has been studied by many authors, who have reported a malignant transformation rate of up to 6.1%.[19,35]

The etiology of lichen planus is unknown, and its association with tobacco intake is controversial.[36,37] However oral lichen planus is now thought to be a cell-mediated immune response to an induced antigenic change in the mucosa, in which basal keratinocytes appear to be the target of T-lymphocytes.[19,38]

The cytotoxic T-lymphocytes utilize various mechanisms involving the granzyme system,[39,41] T-cell restricted intracellular antigen (Tia-1)[42] and cytokines[43] to induce cell death. They also express Fas ligand on their surface and thus can stimulate death receptors present on the surface of keratinocytes.[23,44,45] The cytotoxic-T-lymphocytes are also known to damage DNA (the exact mechanism of which is not clear), thereby activating the tumour suppressor p53 gene, which can either repair the damage by arresting the cell cycle or initiate the cell to undergo apoptosis.[46] Several pro-apoptotic members of Bcl-2 family like Bax, Bak and Apaf-1 (apoptosis activating factor) can be activated by p53 gene. These proteins further initiate the mitochondrial pathway of apoptosis.[47]

An increase in apoptosis has been observed by many authors in oral lichen planus.[48,50] The upregulation of bax and caspase-3 has also been reported by some authors,[51,52,38] though Dekker et al[46] did not observe any significant increase in bax. We could not find any publication in the English literature on caspase-8 and caspase-9 in oral lichen planus.

In oral lichen planus enhanced expression of genes regulating cell proliferation has been reported by some workers.[53,54] However their role has not been studied in detail, though some work on c-erb B-2 gene has been reported,[53,54] K-ras and c-Jun expression have not been studied.

In the present study, we aimed to examine the expression of proteins activating two major pathways of apoptosis (death receptor and mitochondrial pathway) in oral lichen and their relation with proteins regulating cell proliferation.

Material and Methods

The study was undertaken at Maulana Azad Medical College New-Delhi. Thirty clinically diagnosed cases of oral lichen planus and thirty control subjects were included in the study. The oral biopsy specimen was taken from the representative area of each case of oral lichen planus. The diagnosis was confirmed by the presence of characteristic histopathological features of lichen planus. The control group included those subjects having non-specific mild clinical changes on oral mucosa and histology showing minimum inflammation in sub epithelium not specific for any pathology. The study was cleared by the ethical committee of the institute and informed consent was obtained from each subject. The expression of apoptosis, caspase-3, caspase-8, caspase-9, bax, K-ras, c-Jun and c-erbB-2 was studied in all the cases.

Apoptosis

The apoptotic cells were identified by in-situ Terminal TdT-mediated dUTP-biotin Nick-End Labelling (TUNEL) using a commercial kit (cat / q1A33, Oncogene, Boston, U.S.A). In brief, the tissue sections were deparaffinised, rehydrated and treated with Proteinase-K for 20 min at room temperature. The endogenous peroxidase was inactivated by 3% H2b2 in methanol. The tissue sections were incubated with TdT equilibration buffer for 30 min at room temperature, and then with labelling reaction mixture for 60 min at 37^0 C. The 50 X peroxide conjugate was diluted in the blocking buffer (1:50) and tissue sections were treated with it for 30 min at room temperature. All intermediate washing steps were performed by phosphate buffer saline (p1-1-7). The brown colour of the apoptotic cells was then developed by diaminobenzidine. Counterstaining was done with hematoxylin.

Immunohistochemistry

The caspase-8 (Novacastra, Newcastle, U.K), caspase-3 (Novacastra, Newcastle, U.K), caspase-9 (Novacastra, Newcastle, U.K), bax (Santa Cruze, California, U.S.A), K-ras(Santa Cruze, California, U.S.A), c-Jun (Novacastra, Newcastle, U.K) and c-erbB-2 (Novacastra, New castle, U.K) proteins were detected by immunostaining based on avidin-biotin peroxides complex technique.

The tissue section was deparaffinised and rehydrated. The endogenous peroxidase was inactivated with 3% H202 in methanol and non-specific protein binding was blocked by incubation with 5gm milk in 100 m 1 of phosphate buffer saline (pH-7). Slides were then incubated overnight with 40 gl of diluted primary antibody (20:1) at 4° C. Biotinylated horse antimouseIgG secondary antibodies were then applied for 30 min (Novcastra, Newcastle, U.K). The sections were incubated for 30 min with avidin-horse peroxides complex (Novcastra, Newcastle, U.K). All intermediate rinsing steps

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were performed with phosphate buffer saline (pH-7). The brown colour was developed by diaminobenzidine. The positive expression of these antibodies was observed in the cytoplasm.

Statistical Analysis

Cases were divided into two categories: positive and negative depending on the expression of particular protein and apoptosis. The difference in the number of positive cases between the groups was studied by the chi-square test. If any of the expected frequencies was less than five then Fisher's exact test was applied. The association between the groups was studied by the chi-square test for association. A p-value of <0.05 was considered statistically significant.

Results and Observations

Immunohistochemical staining on 30 cases of oral lichen planus showed cytoplasmic positivity in 33 % (10 / 30) of cases for caspase-3 and in 53 % (16 / 30) for caspase-8. The caspase-9 positive cases were 53 % (16 / 30) and those for Bax protein were 67% (20 / 30). About 46 % (14 / 30) cases of lichen planus were positive for K-ras Table 1.

The membrane positivity for c-erb B-2 on co-protein was observed in 40 % (12 / 30) cases and c-Jun nuclear positivity was found in 33 % (10 / 30) cases. Keratinocytes in 40 % (12 / 30) cases of lichen planus specimens showed positive apoptotic signals. Table 1, Results of our control group are summarized in table 1, Figure 1.

A statistically significant increase in the positivity for these proteins and apoptosis was observed in lichen planus cases as compared to the control group Table 1.

We also observed a statistically significant association between apoptosis: caspase-3, caspase-3: caspase-8, caspase-9: bax, caspase-8: caspase-9 and caspase-9: caspase-3. The cases which were positive for apoptosis were also positive for caspases and/or bax, however inverse association was observed between c-Jun:apoptosis and c-erb- 2:apoptosis Table 2.

Table 1.The Percentage Positivity of Apoptosis Activating and Cell Proliferation Proteins

	Control Group (% Positivity) (n = 30)	Lichen Planus (% Positivity) (n = 30)	*P-value (Chi-Square Test)
Apoptosis	6.6 (n=2)	40 (n = 12)	0.005
Caspase-3	3.3 (n=1)	33 (n = 10)	0.005
Caspase-3	6.6 n=2)	53 n = 16)	<0.001
Caspase-3	0.0 (n=0)	53 (n = 16)	<0.001
Bax	3.3 (n = 1)	67 (n = 20)	<0.001
c-Jun	10 (n = 3)	33 (n = 10)	0.03
c-erB-2	10 (n = 3)	40 (n = 12)	0.009
K-ras	10 (n = 3)	46 (n = 14)	0.004

*All P-Values were significan

Table 2.Association between Markers of Apoptosis & Cell Proliferation in Oral Lichen Planus

Association Pair	P-value (Chi-Square Test)
Apoptosis	<0.001
Caspase-3	<0.001
Caspase-3	<0.001
Caspase-3	0.024
Bax	0.050
K-ras and apoptosis	0.300
c-Jun	0.024#
c-erB-2	0.024#
# inverse association	

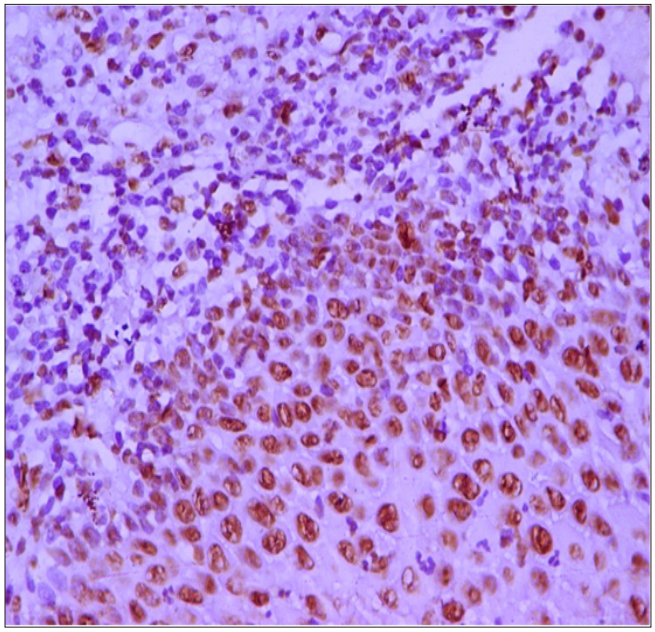

Figure 1.Expression of Apoptosis in Oral Lichen Planus

Discussion

Oral lichen planus is a chronic inflammatory disease, in which basal epithelial cells of the oral mucosa are attacked by T-lymphocytes.[19,38] The target cells trigger a series of complex molecular mechanisms that may arrest the cell cycle for DNA repair, or induce apoptosis to eliminate cells with severally damaged DNA.[46] There are two major pathways by which the apoptotic demise of the cell is initiated, extrinsic pathway (death receptor) and intrinsic pathway (mitochondrial).[23,47]

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The activation of the Fas system on T-lymphocyte in oral lichen planus has been studied by various workers.[23,44,45] The Fas ligand expressed by T-lymphocytes binds to the Fas receptor present on the surface of the epithelial cells. This results in the transduction of a signal that activates the death receptor pathway.[23,44,45] We have studied the expression of proteins involved in this pathway in oral lichen planus. A significant increase in caspase8 positivity was observed, similar increase was also observed in caspase-3 and apoptosis-positive cells as compared to the control subjects. Though we did not find any study of caspase-8 in oral lichen planus, the increase in caspase-3 and apoptosis positivity was also reported by other workers.[48,51] The association of caspase-3 with caspase-8 and with apoptosis was significant in the present study, however contradictory results have been reported by some workers.[48] Thus our findings are consistent with the hypothesis that the apoptosis by death receptor pathway in oral lichen planus is being activated by fas ligand expressed on the cytotoxic T-lymphocytes.

In literature, the reports regarding bax positivity in oral lichen planus are conflicting.[51,52,38,46] In the present study the up-regulation in Bax and caspase-9 has been observed. Some authors have suggested, that the increased Bax expression may be due to its activation by tumour suppressor p53 gene which gets activated due to DNA damage by cytotoxic T-lymphocytes.[46]

The caspase-9 can also be activated by the death receptor pathway involving caspase-8, through pro-apoptotic molecule Bid.[55] A significant association of caspase-9 with caspase-8 in the present study may suggest the activation of this pathway by T-lymphocytes in oral lichen planus.

Thus we may summarize that cytotoxic T-lymphocytes can activate multiple pathways of apoptosis in oral lichen planus.

The substantial increase in apoptotic death of epithelial cells in oral lichen planus by cytotoxic T-lymphocyte could be harmful to the epithelium' however, some authors have demonstrated that epithelial cells in oral lichen planus frequently respond by evolving a resistance molecular mechanism that can resist the cell death and or stimulate the epithelial cell proliferation.[53,54] Proto-on genes acting as growth factor receptors, signal transducers and transcription factors play a central role in controlling cell proliferation. A significant increase in c-erb B-2 (growth factor receptor), K-ras (signal transducer) and c-Jun(transcription factor) in the present study suggests the presence of a possible mechanism that might lead to the maintenance of the epithelial structure. The alteration in the expression of proto-oncogene regulating cell proliferation may lead to malignant transformation in oral lichen planus.

In conclusion, we found increased apoptosis in oral lichen planus. The apoptosis in oral lichen planus occurs via both extrinsic and intrinsic pathways, and the epithelium responds by increased expression of proteins involved in cell proliferation.

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Conflict of Interest: None

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