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ROLE OF BCL-2 IN THE PATHOGENESIS OF PSORIASIS

Pathology

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ABSTRACT

Psoriasis is a common inflammatory skin disease characterized by the epidermal hyperplasia and greatly accelerated turnover. A complex mechanism involving immune dysregulation, enhanced keratinocytic proliferation, inflammation and angiogenesis has been proposed as the pathogenic mechanism of psoriasis. It has been postulated that the increased epidermal thickness and altered tissue architecture observed in psoriasis may be related to an abnormality in the apoptotic pathway. There is aberrant epidermal expression of apoptosis related molecules leading to the suppression of the apoptotic process, while suppression of apoptosis of T lymphocytes leads to the chronic and relapsing character of psoriasis. There is a number of such apoptosis related molecule out of which Bcl-2 gene has gained a unique importance as the inhibitor of apoptosis. In the present study both lesional and non-lesional skin biopsy samples from 30 patients with psoriasis were studied for expression of Bcl-2 protein by immunohistochemical staining.

KEYWORDS

bcl-2, Psoriasis, Dermal lymphocytes

INTRODUCTION

Psoriasis is a common chronic disease of skin characterized by recurrent exacerbation and remission. It is a genetically determined, inflammatory and proliferative disease of skin, the most characteristic lesions consisting of sharply demarcated, dull-red, scaly plaques, covered with fine silvery grey scales particularly involving the extensor prominences and the scalp. The disease is enormously variable in duration and extent with several morphological variants.[1]

Psoriasis is characterized by abnormal hyperproliferation of the epidermis.[2] Psoriasis is unique in this sense as it represents excessive, but controlled cellular proliferation and inflammation. Psoriasis affects approximately 2% of worldwide population.[3] Its prevalence in India is estimated to be 0.7%.[4]

The primary pathogenetic mechanism for psoriasis is still unknown. It has been described as a T-cell mediated disease that involves keratinocytic proliferation along with inflammation and angiogenesis. Keratinocytes, fibroblasts, antigen presenting cells, T-cells and endothelial cells have all been proposed as the candidate for the primary defect.[5]

Recruitment of lymphocytes to the papillary dermis is an important factor in the pathogenesis of psoriasis.[6] Both CD4 lymphocytes (found predominantly in dermis) and CD8 lymphocytes (found predominantly in epidermis) appear to be involved. The lymphocytes bind to the endothelial cells in venules as a consequence of the enhanced expression of various adhesion molecules by endothelial cells.[7] The kertinocytic proliferation is mainly mediated by cytokines produced by lymphocytes e.g. IL-8, TNF-alpha and interferon–gamma. These factors produce an alteration in the turnover time for the epidermis: 3-4 days in psoriasis as compared with the usual 13 days in the normal skin.[8]

Bcl-2 has been considered to be the cell death suppressor gene that regulates the apoptosis (Programmed cell death). The Bcl-2 protein is located in the periphery of mitochondria on the perinuclear membrane and the endoplasmic reticulum.[9] The Bcl-2 protein serves as docking protein to Apaf-1. Thereby, this family of protein interacts with each other and prevent formation of cyt. C/ Apaf-1 complex that activate caspase and subsequently activate caspase 3 resulting in apoptosis. The overexpression of Bcl-2 protein suppresses the DNA fragmentation that occurs in apoptosis and is associated with decreased level of cytosolic calcium and increased level of mitochondrial calcium. This indicates role of Bcl-2 protein in the regulation of intracellular Ca^{2+} distribution. The role of Bcl-2 protein as an antioxidant to prevent cell death is also known.[10]

Bcl-2 protein expression is mainly observed in cell populations with a long life and/or proliferating ability such as duct cells in exocrine glands, basal keratinocytes, cells at the bottom of colon crypts, and neurons. In the skin of both adult and embryo and also embryonic kidney and cartilage, *bcl-2* expression was observed in cells which were undergoing morphological transition from undifferentiated stem cells to committed precursor cells. These observations support the view that the *Bcl*-2 gene may have an important role in cell development, maturation, and the path to terminal differentiation.[11]
It has been implicated in several diseases including several epithelial tumors, breast carcinoma, prostatic neoplasms, autoimmunity as well as melanoma and cutaneous basal cell carcinoma.[12]

Expression of Bcl-2 protein can be detected by immunohisto chemistry.

MATERIAL AND METHODS

The study was performed on thirty skin biopsies with Psoriasis received in the department of Pathology, Govt. Medical College, Amritsar. The tissues were formalin fixed, paraffin embedded and stained with routine haematoxylin and eosin and histological diagnosis was made. Then, Immunohistochemistry (IHC) was performed using avidin-biotin-peroxidase complex (ABC) technique. New sections of 3-5 µm thickness for each case were then cut from paraffin-embedded blocks and mounted on freshly prepared 0.01% poly-1-lysine-coated slides. Slides were dried overnight at 37°C, dewaxed in xylene, and then gradually rehydrated. Endogenous peroxidase activity was blocked using 0.3% hydrogen peroxide in methanol for 10 min followed by three washings in phosphate buffered saline (PBS), and then antigen retrieval was achieved in a pressure cooker (4 times, 5 min each; 0.1 M citrate buffer, pH 6.0). The sections were then brought to room temperature and immersed in PBS followed by washing in phosphate buffer saline and 2 drops of 3% H_2O_2 and were then incubated for 10-30 minutes. Two drops of primary monoclonal antibody was added and incubated for 60 minutes. After washing with PBS, sections were again incubated with linked antibody for 30 minutes. Enzyme conjugate was added and incubated for 30 minutes. Each step was followed by washing with PBS twice. One tablet of DAB was dissolved in reagent and the sections were incubated with this for 6-8 minutes. All incubations were done in a moist chamber. Sections were washed in deionised water for 3 minutes. Haematoxylin counterstaining was done for 2-5 minutes and sections were washed under running tap water and then dehydrated in ascending concentrations of alcohol, cleared and mounted with mounting media.

Positive control tissue had brown colored end product at site of target antigen in the cytoplasm of the cells. Negative control sections did not have any colored product.

In dermal lymphocytes, Bcl-2 scoring was done according to Yildiz et a1[13] as follows

0 = No staining of lymphocytes
1 = < 25% staining of lymphocytes
2 = 26-50% staining of lymphocytes
3 = 51 -75% staining of lymphocytes
4 = > 75% staining of lymphocytes

The data was compiled and analysed statistically.

Observations:

TABLE1 Comparison of bcl-2 positivity in lesional and non-lesional lymphocytes

	No. of cases	Bcl-2 score				
		0	1	2	3	4
Lesional lymphocytes	30	5	7	13	5	0
Non lesional lymphocytes	30	26	04	0	0	0

χ^2=33.04 df=3 p=< 0.001

In psoriatic lesional dermal lymphocytes, out of 30 samples, 5 cases did not show any staining for bcl-2 in dermal lymphocytes. The remaining 25 cases showed cytoplasmic brown staining with percentage positivity ranging from less than 25% to upto 75%. Accordingly 5 (16.7%) cases had score 0, 7 (23.3%) cases had score 1, 13 (43.3%) scored 2, while 5 (16.7 %) scored 3, none of the cases had score 4.

In non lesional biopsy samples out of 30 cases 26 cases did not show any staining for Bcl-2 in dermal lymphocytes. The remaining 4 cases showed cytoplasmic brown staining in less than 25% of dermal lymphocytes. Accordingly 26 (86.7%) had score 0, while 4 (13.3%) cases had score 1.

On comparing the level of Bcl-2 expression in lesional and non lesional dermal lymphocytes, it was found that Bcl-2 expression was significantly higher in lesional dermal lymphocytes as compared to non lesional samples (p value<0.05).

DISCUSSION

Bcl-2 is an important molecule that prevents apoptosis. The expression of Bcl-2 was significantly higher in dermal lymphocytes in psoriatic lesions as compared to non lesional skin. Bcl-2 being an antiapoptotic molecule, its overexpression in dermal lymphocytes indicates blockage in apoptotic removal of these lymphocytes leading to their prolonged survival. Removal of the excess cells after the completion of an inflammatory process is essential in the regulation of an inflammatory response, failure to do so can result in a prolonged inflammatory response. The same mechanism operates in psoriatic lesions leading to prolonged inflammatory and chronic nature of psoriasis.

Similar observations were made by Domyati et al who found that Bcl-2 expression **in psoriatic lymphocytes was significantly higher in lesional dermal lymphocytes than in non-lesional dermal lymphocytes.** They detected **Bcl-2 expression in the dermal lymphocytes of 17 (56.7%) biopsies out of 30 biopsies from psoriatic lesions and it** was not detected in the dermal lymphocytes of non-lesional skin biopsies **(p<0.001).**[14]

Similarly Yildiz et al found that there was overexpression of bcl-2 staining in dermal lymphocytes of psoriatic skin biopsy samples as compared to the control and noticed Bcl-2 staining in 20 (71.4%) out of 28 samples of psoriatic lesional biopsies as compared to the control which did not show any Bcl-2 staining. Out of 20 positive cases two (10%) cases were 4+, three (15%) cases were 3+, five (25%) cases were 2+ and 10 (50%) cases were 1+.[13]

Hussein et al in their study found that Bcl-2 immunoreactivity in the lymphocytes showed statistically significant up-regulation in non tumorigenic, pre tumorigenic and tumorigenic conditions. In case of psoriasis vulgaris , bcl-2 average weighted score was 3.0 ±0.39 as compared to the normal skin with Bcl-2 average score of 2.0 ±0.0 (p value <0.05).[15]

SUMMARY AND CONCLUSIONS

The antiapoptotic molecule, Bcl-2 expression in dermal lymphocytes was significantly higher in psoriatic lesions as compared to non lesional skin. This indicates blockage in apoptotic removal of these lymphocytes occur, leading to their prolonged survival. Removal of the excess cells after the completion of an inflammatory process is essential in the regulation of an inflammatory response, failure to do so can result in a prolonged inflammatory response. The same mechanism operates in psoriatic lesions leading to prolonged inflammatory and chronic nature of psoriasis

In conclusion, the overexpression of Bcl-2 in dermal lymphocytes by its antiapoptotic action leads to increased lymphocyte survival resulting in prolonged inflammation which relates to the chronic and relapsing character of psoriasis and thus may play an important pathogenetic role in maintenance of psoriatic lesions.

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