Expression of apoptosis regulating proteins p53 and bcl-2 in psoriasis

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ABSTRACT

Background: Dysfunctional apoptosis has an important role in the development of several skin diseases. Psoriatic keratinocytes possess an enhanced ability to resist apoptosis, which might be one of the key pathogenetic mechanisms in psoriasis. P53 and bcl-2 are two proteins which control apoptosis. Several studies have evaluated the expression of these two proteins in the psoriatic skin, but the results are controversial.

Methods: Fifty-eight cases of psoriatic skin biopsies were studied, and the grade of p53 and bcl-2 immunostaining was correlated with the histopathological indices of severity.

Results: Bcl-2 expression in the epidermis strongly correlated with the expression in the basal cells and lymphocytes \((P = 0.001 \text{ and } 0.035)\). There was no correlation with epidermal hyperplasia or with p53 expression in the three compartments. Bcl-2 expression in the basal layer correlated with the p53 expression in the epidermis \((P = 0.027)\), basal layer \((P = 0.015)\) and the lymphocytes \((P = 0.034)\). There was a strong correlation among the p53 expression in all the compartments. There was also a weak correlation of the p53 expression in the epidermis with the epidermal hyperplasia \((P = 0.042)\). Conclusions: Bcl-2 does not appear to play an important role in the apoptotic process in psoriasis. In contrast, it is likely that p53 has a far more important role to play. Mutation analysis of the p53 protein is necessary to evaluate if the protein has mutated or if it is of the wild type.

KEY WORDS: Bcl-2, p53, psoriasis

INTRODUCTION

Apoptosis is a process of programmed cell death. The concept of apoptosis was described by Kerr et al., who described apoptosis as an active process morphologically characterized by cell shrinkage, nuclear condensation, cellular fragmentation, and phagocytosis by neighboring macrophages and dendritic cells.\(^1\) Apoptosis is important in embryonic development, balancing cell number in continuously renewing tissues and immune system development.\(^2\) In the skin, apoptotic cell death regulates keratinocyte proliferation and formation of stratum corneum. The balance between cell death and cell proliferation maintains homeostasis of the epidermal compartment.\(^3\)

Dysfunctional apoptosis has an important role in the development of several skin diseases\(^2,4\) including toxic epidermal necrolysis and graft-versus-host disease. Psoriasis is a disease which is associated with decreased apoptosis.

Psoriatic keratinocytes possess an enhanced ability to resist apoptosis, which might be one of the key pathogenetic mechanisms in psoriasis.\(^5\) The process of apoptosis is controlled by bcl-2 family proteins including several pro- and anti-apoptotic proteins.\(^6\) Authors have reported an overexpression of the bcl-2 protein in psoriasis whereas other authors have found that there is no expression of bcl-2 in psoriasis.\(^7,8\) P53 is a phosphoprotein, which shows transcription factor-like properties.\(^9\) P53 immunoreactivity has also been found in several inflammatory skin diseases, such as psoriasis, lichen planus, chronic dermatitis, and lupus erythematosus.\(^10\) Like the bcl-2 expression, in psoriasis, the results of the p53 expression are frequently controversial.

MATERIALS AND METHODS

This study was designed as a prospective study and included skin specimens of 58 patients with psoriasis vulgaris diagnosed at Pathology Department of a large tertiary hospital. The study was...
RESULTS

Demographic variables
Fifty-eight cases were analyzed in the present study. The means age was 40.7 years with a range of 13–76 years. Thirty-six males and 22 females comprised the study population.

Correlation of bcl-2 immunostaining in the epidermal cells with different parameters
The bcl-2 immunostain in the cytoplasm of the epidermal cells showed a strong correlation with the grade of bcl-2 immunostain in the basal cells (P = 0.001) and the mononuclear cells (P = 0.035) [Figure 1]. There was no correlation with the grade of p53 immunostaining in the epidermis (P = 0.958), basal cells (P = 0.309), or in the lymphocytes (P = 0.167). There was also no correlation with the grade of epidermal hyperplasia (P = 0.735).

Correlation of bcl-2 immunostaining in the basal cells with different parameters
There was no correlation between the grade of the bcl-2 immunostaining in the cytoplasm of the basal cells with the grade of bcl-2 immunostaining in the mononuclear cells (P = 0.935). There was a strong correlation with the grade of p53 immunostaining in the lymphocytes (P = 0.034), epidermal cells (P = 0.027) and grade of p53 immunostaining in basal cells (P = 0.015) [Figure 2]. There was, however, no correlation with the grade of epidermal hyperplasia (P = 0.393).

Correlation of bcl-2 immunostaining in the lymphocytes with different parameters
The bcl-2 immunostaining in the lymphocytes showed a strong correlation with the grade of p53 immunostaining in the epidermal cells (P = 0.036). There was, however, no correlation with the grade of p53 immunostaining in the basal cells (P = 0.632) or in lymphocytes (P = 0.454). There was also no correlation with grade of epidermal hyperplasia (P = 0.100).

Correlation of p53 immunostaining in different compartments with different parameters
The p53 immunostaining in the epidermal cells showed a strong correlation with the grade of p53 immunostaining in the basal cells (P = 0.001) and in the lymphocytes (P = 0.001). There was, however, no correlation with the grade of epidermal hyperplasia (P = 0.291). The p53 staining in the basal cells also showed a strong correlation with the p53 staining in the lymphocytes (P = 0.001).

DISCUSSION
Psoriasis is a common chronic inflammatory skin disease characterized by hyperproliferation and incomplete differentiation of epidermal keratinocytes.[11] Apoptosis or programmed cell death plays an important part in the pathogenesis of psoriasis.

Data regarding the expression of bcl-2 family proteins in psoriatic plaques are controversial, and workers have reported conflicting

Statistical analysis
The sample size was calculated taking \( \alpha \) (type I) error as 5%, the confidence interval of 95% and the power of the study as 80%. The minimum sample size was calculated using the EPI Info 2002 software. The sample size was calculated was 56.

The results of the study were statistically analyzed using SPSS 13.0 statistical package program (Statistical Package for Social Sciences, Lead Technologies Inc., USA). The descriptive data were given as mean and standard deviation. The Pearson's correlation coefficient was used for comparison the differences between groups. A value of \( P < 0.05 \) was considered to indicate statistical significance.
reports. Some groups have reported an overexpression of the bcl-2 protein, whereas others observed no expression of the anti-apoptotic bcl-2 molecule in psoriatic epidermis. An overexpression of bcl-xL and Bax has been reported in the psoriatic epidermis. This in itself is conflicting because bcl-xL is anti-apoptotic, and Bax is pro-apoptotic.

In the present study, we noted that the bcl-2 expression in the basal cells correlated with the p53 expression in the epidermal cells, basal cells, and lymphocytes. The kinetics of the basal cell is different from the rest of the epidermal cells. Bcl-2 is anti-apoptotic, and p53 is pro-apoptotic and it stands to reason that there should be an inverse correlation between the expression...
of these two proteins and not a linear correlation. The fact that they are linearly correlated means that both pro- or anti-apoptotic processes are going on simultaneously in the basal cells. This apparent dichotomy has been reported by other authors.\[12\]

We also noted that there was no correlation between the bcl-2 overexpression and epidermal hyperplasia. An expression of bcl-2 overexpression should correlate with epidermal hyperplasia since bcl-2 is an anti-apoptotic protein. The absence of this correlation suggests that bcl-2 is a relatively unimportant protein in the pathogenesis of psoriasis. Other authors have reported a weak expression of bcl-2 in the basal cells suggesting that bcl-2 is perhaps a relatively unimportant protein in the pathogenesis of psoriasis.\[7,15\]

The p53 immunostaining in the epidermis correlated weakly with the grade of epidermal hyperplasia. These finding suggest that p53 has a bigger role to play than bcl-2 as far as the apoptotic process in the psoriatic skin is concerned. These findings are similar to what is reported in the literature. Baran et al.\[16\] have reported that the percentage of p53 cells were significantly higher in the specimens from gave quite different results. We found that the grade of p53 staining in the basal cells correlated strongly with the p53 immunostain in the rest of the epidermis and the lymphocytes. We also found that there was a weak correlation between the grade of p53 immunostaining in the epidermal cells and the grade of lesional psoriatic skin than in normal skin or nonlesional skin. Other authors have reported that p53 is overexpressed in the keratinocytes of the psoriatic epidermis.\[17-19\]. The other point to be determined is whether the p53 is of the wild type or whether it has mutated. It has been suggested that the increased p53 protein synthesis in psoriasis is of the wild-type as a normal biological response to a higher frequency of DNA damage. Studies have shown that there is no p53 mutation in psoriasis. Analysis of the p53 mutations will determine if they protein has mutated or if it is of the wild type.

CONCLUSION

Our study has shown that the bcl-2 protein perhaps does not play a major role in the apoptotic process. P53 is important in the apoptotic process in the psoriatic skin. P53 and bcl-2 expression does not show a correlation with each other suggesting that proteins other than bcl-2 are important in the apoptotic process.

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Conflicts of interest
There are no conflicts of interest.

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