Mast Cells in Cutaneous Wound Healing

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Maria Huttunen defended her thesis on December the 12th, 2003, in the Faculty of Medicine of the University of Kuopio. Faculty opponent was Professor Aarne Oikarinen (right), Department of Dermatology, University of Oulu, Finland and chairman was Professor Ilkka Harvima (left), Department of Dermatology, University of Kuopio, Finland.

ABSTRACT

Mast cells are suggested to participate in wound healing, but their specific role has remained obscure. Mast cells are a rich source of inflammatory mediators, such as histamine, proteoglycans, the proteases tryptase and chymase, lipids, growth factors and cytokines. Among these mediators, there are many that have effects on cell growth, tissue turnover and repair. The aim of this study was to characterize the functions of mast cells in wound healing by studying mast cell activation in normal skin and the alterations undergone by mast cells in normally healing wounds, and investigating the effects of mast cell mediators on cultured keratinocytes and on epithelialization in vitro. The potential roles of mast cells and their mediators were explored also in chronic leg ulcers.

The microdialysis technique was used to monitor histamine release in skin following skin challenge with neuropeptides substance P (SP), vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), and capsaicin. SP and VIP, but not CGRP, caused mast cell degranulation and histamine release. Capsaicin, a neuropeptide releasing agent, did not cause any substantial histamine release, suggesting infrequent morphological contacts between mast cells and sensory nerves in normal human skin.

In normally healing wounds, the numbers of mast cells, especially those with chymase activity, decreased in number and could not be found in the epithelialization margin. In chronic ulcers, mast cells were numerous in the perilesional skin and often in contact with the epithelial margin, and chymase was partially inactivated, as detected enzyme- and immunohistochemically. The expression of stem cell factor (SCF, a mast cell growth factor) and Kit (its receptor on mast cells) showed significant alterations during wound healing. The numbers of dermal cells expressing SCF were markedly increased on day 1 after wounding and declined thereafter, whereas the expression of Kit increased steadily throughout wound healing. In chronic ulcers, most of the mast cells were Kit-positive, while SCF-positive cells were numerous in the wound bed. Thus, in chronic ulcers, there seems to be a potential for interaction between SCF and the Kit receptor, leading to mast cell proliferation, migration and degranulation. In contrast, only temporary SCF-mediated mast cell activation seems to occur during normal wound healing.

Significant levels of soluble tryptase activity and histamine, but low levels of chymase activity, were measured in samples washed from chronic leg ulcers. Parallel with this result, no tryptase-inhibiting activity, but clear chymase-inhibiting activity, was detected in the wash samples.

Histamine and heparin were inhibitory to keratinocytes in vitro. They inhibited both the ^{3}H-thymidine incorporation into keratinocytes and the keratinocyte outgrowth from skin specimens. A lysate from HMC-1 mast cells inhibited keratinocytic and epithelial growth as well. Purified human tryptase had no significant effect on the growth and adherence of keratinocytes in various experimental settings. In contrast, chymase efficiently detached monolayer keratinocytes or caused marked destruction of the developing epithelium within 2 days. Since mast cells were accumulated at the epithelial margin of chronic leg ulcers, these findings provide evidence that mast cells may participate in the pathophysiology of impaired epithelialization in chronic wounds.

Medical Subject Headings: mast cells; wound healing; skin; leg ulcer; chronic disease; stem cell factor; serine endopeptidase; protease inhibitors; keratinocytes; histamine; heparin; microdialysis; neuropeptides; psoriasis.

Genetic and Lifestyle Determinants in Skin Cancer: Study of the Nationwide Twin and Cancer Registry Cohorts

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Objective

To assess the patterns in familial aggregation and risk factors in basal cell carcinoma (BCC) and other skin cancers in Finland.

Subjects and Methods

The first study cohort was identified from the files of the nationwide population-based Finnish Cancer Registry. The follow-up for the subsequent primary neoplasms started on the first day of the month following the date of diagnosis of the first BCC, and ended at the time of death, emigration or the closing date of the study (December 31, 1995), whichever occurred first. The standardized incidence ratios (SIR) were calculated by sex, 5-year age group, calendar period and subsite of BCC.

Three other studies are based on the Finnish Twin Cohort Study, which consists primarily of adult same-sexed twin pairs born before and

with both members alive in 1967. Familial aggregation was estimated by calculating the numbers of twin pairs concordant and discordant for BCC, probandwise and pairwise concordance rates, tetrachoric correlations and relative risks in 1953–1996. The components of variance in susceptibility to BCC were also estimated in 1976–96 based on structural-equation model fitting. For malignant skin cancers the SIRs were calculated in twins in Finland during 1976–1997. Logistic regression was used to assess the effect of selected social and lifestyle factors on the onset of BCC.

Results and Discussion

The nationwide study cohort included 71,924 subjects with BCC diagnosed during 1953-1995. The overall cancer incidence was significantly elevated during all follow-up periods after the BCC diagnosis. The pattern was similar after exclusion of skin cancers, the SIR being highest during the first year. Subjects who were less than 40 years of age at the time of diagnosis of BCC had a significantly higher relative risk for subsequent cancer than did those aged 40 or more. Some of the increase in the risk of skin cancer after an initial diagnosis of BCC is likely to be due to the enhanced diagnostics and social class selection.

The risk of skin cancer in an unselected adult twin population did not differ from the risk in the population at large. Secondly, the patterns of pairwise occurrence of BCC were most consistent with the concept that environmental influences are of primary importance in the aetiology of the disease. The role of lifestyle differences as putative risk factors for BCC were examined in a co-twin control study of 333 discordant twin pairs. In contrast to some previous studies, a statistically significant risk increase for smoking was found in women; pertinent in dizygotic but not in monozygotic women.

Conclusions

The present study strongly suggests that environmental and not hereditary effects are most important in the development of cutaneous malignancies in the white population with low levels of sun exposure in Finland. However, the increase of several non-cutaneous cancers suggests a generalised carcinogenic role for some of the BCC risk factors.

Key words: basal cell carcinoma; squamous cell carcinoma; melanoma; subsequent cancers; diseases in twins; disease susceptibility; case-control studies; cohort studies; genetics; epidemiology; Finland.