Overexpression of Matrix Metalloproteinases, Chemokines, and Chemokine Receptors Relevant for Metastasis in Experimental Models Not an Indication of Lymph Node Metastases in Human Melanoma

Morphologic characteristics such as tumor thickness and ulceration are the major accepted indicators of risk for metastatic spread. Since matrix metalloproteinases and chemokines and their receptors are involved in the complex process of metastasis, we tested whether their expression predicts the risk of melanoma progression. To this end, the relative messenger RNA (mRNA) expression of chemokine receptors CCR7 and CXC4, the chemokine CXCL8, and the matrix metalloproteinases MMP2 and MT1-MMP in primary cutaneous melanomas from 28 patients was correlated with the presence of micrometastases in the respective sentinel lymph nodes.

Methods. We gained approval from our local ethics committee, and analyses were performed with the patients’ informed consent. Primary tumors were trimmed to remove most of the surrounding unaffected skin, and total RNA was isolated from frozen tissue sections. After complementary DNA was generated from this RNA, relative expression of CCR7, CXC4, CXCL8, MMP2, and MT1-MMP was determined by real-time polymerase chain reaction and the comparative delta-delta threshold cycle (ΔΔCt) method where glyceraldehyde-3-phosphate dehydrogenase served as endogenous control. The results were statistically tested after log-normal transformation using the 2-tailed nonpaired t test.

Results. For CXC4 (P = .01) and MMP2 (P = .04), an inverse relationship between mRNA expression and presence of lymph node metastasis was detected (Figure). Primary tumors associated with concurrent lymph node metastasis, while not reaching statistical significance, also showed lower expression of CCR7 (P = .06) and MT1-MMP (P = .09). For CXCL8 (P = .96), no correlation was observed.

Comment. The statistically significant inverse correlation of the expression of genes known to promote metastasis (CXC4 and MMP2) and the presence of lymph node micrometastases was unexpected. For example, Müller et al detected an increased expression of CXC4 and CCR7 in human melanoma cells compared with primary melanocytes. In a murine melanoma model, however, CXC4 expression did not enhance occurrence of lymph node metastasis.1

Notably, cell signaling is influenced not only by the amount of expressed chemokine receptors or their ligands but also through regulatory mechanisms. Indeed, despite high expression of CXC4 on germinal center T cells, their migration to CXCL12 was diminished owing to follicular dendritic cell–mediated expression of regulators of G protein signaling 13 and 16.3 In addition, tumor cells are highly flexible, ie, they can change from proteolytic migration to proteolysis-independent movement in an ameboid manner.4 Furthermore, heterogeneity of tissues has to be taken into account; in contrast to tumor cell lines, tumors consist of different proportions of tumor, fibrocytic, vascular, and inflammatory cells. Therefore, the variances in mRNA expression could partly be due to variances in cell composition. Thus, polymerase chain reaction analyses of microdissection samples should reflect the cytokine expression in single cells more accurately.

Nevertheless, since tumor cells and surrounding host cells form a complex environment, the investigation of the whole tumor is in accordance with physiologic conditions. Such an analysis, however, forecloses identification of individual cells characterized by overexpression of a given mRNA, which may be essential for the metastatic potential. In addition, similar RNA levels may result in different protein expression by differences in the protein turnover, ie, translation and degradation. Therefore, our results do not exclude the relevance of the in-
vestigated factors for promoting metastasis but demonstrate the unsuitability of global analysis of these transcripts for determining patient prognosis.

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Methods. Anonymous surveys were sent to 122 dermatology department chairpersons and/or chiefs. Chairpersons were identified through medical school Web sites and publications of the American Medical Association.3 Survey questions focused on demographics, tenure, and future plans of current department chairpersons. In addition, questions were asked about prevailing attitudes in the department toward academic medicine, faculty retention, and the adequacy of the pool of candidates for future leadership positions. Analysis was performed using t tests on continuous variables (Excel 2003; Microsoft Inc, Redmond, Washington). P < .05 was considered significant.

Results. Sixty percent of the surveys were returned (n=73). The reported average age of current chairpersons was 56 years, and the average age at which they became chairperson was 45 years. Chairpersons characterized their career focus as listed in the Table. Most chairpersons (68%; n=50) did not feel that there was an average age at which faculty members left academia. However, of the 31% (n=23) who did feel that academics left at a certain age, 64% (n=15) believed that faculty members left before age 40 years. Chairpersons identified several leading factors that motivated faculty members to leave academia, including the pressure to publish (cited by 68% of chairpersons [n=50]), financial concerns (60%; n=44), and family concerns (31%; n=23) (Table). Moreover, 66% of chairpersons (n=48) did not feel academic salaries in their area were competitive with salaries in private practice. By contrast, teaching was the primary reason chairpersons cited for faculty members remaining in academia (Table).

The anticipated average retirement age of the chairpersons was 62 years. Five chairmanship positions (7%) were reported as open at the time of the survey; 14% of chairpersons (n=10) were planning to resign within the year; and 32% (n=23) anticipated resigning within 3 years. Therefore, a 10% turnover rate in chairmanships per year is likely to persist. Current chairpersons felt that an average of 1.4 faculty members within their department would be appropriate chairperson candidates within 1 to 5 years.

Leadership Workforce in Academic Dermatology

Growing concern has been voiced at recent Association of Professors of Dermatology meetings that the clinical, teaching, and research demands of academic dermatology may strain and diminish the workforce of current academic dermatologists.1,2 A depletion of faculty members aged approximately 45 years could reduce the pool of potential candidates for chairpersons and other positions of leadership within dermatology. The present study was designed to characterize current dermatology department and division chairpersons and to examine the current number of open dermatology chairmanships in the United States, their rate of turnover, and the presence of suitable candidates.

Figure. Significantly decreased expression levels of chemokine receptor CXCR4 (A) and matrix metalloproteinase MMP2 (B) were found in primary melanomas of patients with positive sentinel lymph nodes (SLNs) (n=11) compared with SLN-negative patients (n=17). ΔΔCt indicates delta-delta threshold cycle. The y-axes represent the amounts of the respective messenger RNA (calculated as 2−ΔΔCt). A superficial spreading melanoma with a tumor thickness of 0.65 mm from a clinically SLN-negative female patient served as the calibrator. The mean values for each group are represented as horizontal lines.

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