ORIGINAL ARTICLE

Basal Cell Carcinoma

Stressful Life Events and the Tumor Environment

Scan for Author Audio Interview

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Context: Child emotional maltreatment can result in lasting immune dysregulation that may be heightened in the context of more recent life stress. Basal cell carcinoma (BCC) is the most common skin cancer, and the immune system plays a prominent role in tumor appearance and progression.

Objective: To address associations among recent severe life events, childhood parental emotional maltreatment, depression, and messenger RNA (mRNA) coding for immune markers associated with BCC tumor progression and regression.

Design: We collected information about early parent-child experiences, severe life events in the past year as assessed by the Life Events and Difficulties Schedule, depression, and mRNA for immune markers associated with BCC tumor progression and regression from patients with BCC tumors.

Setting: University medical center.

Participants: Ninety-one patients with BCC (ages, 23-92 years) who had a previous BCC tumor.

Main Outcome Measures: The expression of 4 BCC tumor mRNA markers (CD25, CD3ε, intercellular adhesion molecule 1, and CD68) that have been linked to BCC tumor progression and regression were assessed in BCC tumor biopsy specimens.

Results: Both maternal and paternal emotional maltreatment interacted with the occurrence of severe life events to predict the local immune response to the tumor (adjusted $P = .009$ and $P = .03$, respectively). Among BCC patients who had experienced a severe life event within the past year, those who were emotionally maltreated by their mothers ($P = .007$) or fathers ($P = .02$) as children had a poorer immune response to the BCC tumor. Emotional maltreatment was unrelated to BCC immune responses among those who did not experience a severe life event. Depressive symptoms were not associated with the local tumor immune response.

Conclusions: Troubled early parent-child relationships, in combination with a severe life event in the past year, predicted immune responses to a BCC tumor. The immunoreactivity observed in BCCs and the surrounding stroma reflects an anti–tumor-specific immune response that can be altered by stress.

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Stressful events and the negative emotions they generate can dysregulate immunity sufficient to produce clinically significant alterations.[1] Acute and chronic stressors can impair vaccine responses, slow wound healing, promote inflammation, and dampen markers of both innate and adaptive immune function.[2-6] Those who experienced adverse childhood events are particularly sensitive to subsequent stressors.[7-10]

Converging evidence suggests that highly stressful events early in life can have long-term consequences for immune system regulation. Childhood maltreatment has been associated with elevated inflammation and higher antibody titers to herpes simplex virus type 1 (reflecting poorer cellular immune function).[11-15] Child maltreatment also has been linked to multiple diseases, including cancer; immune dysregulation likely contributes to these effects.[16]

Skin cancer, the most common cancer in the United States, is more prevalent than all other malignant tumors combined.[17,18] The incidence of basal cell carcinoma (BCC), the most common skin cancer, has been doubling every 14 years.[19] The risk of subsequent BCCs after an initial tumor is substantial, with 44% of patients developing additional lesions within 3 years.[20] Risk factors for the first or index BCC include age, childhood sun exposure, fair skin, and male sex; however, subsequent tumors are not reliably related to these variables.[20,21]

The immune system plays a prominent role in BCC tumor appearance and progression.[22] A significant increase in the

expression of CD3ε (total T cells) and CD25 (interleukin [IL] 2 receptor) has been observed in actively regressing tumors compared with those showing no current or past regression.[23] Furthermore, increased expression of intercellular adhesion molecule 1 (ICAM-1) and infiltration of $CD68^+$ cells (macrophages) have been described during BCC tumor regression after treatment with imiquimod (a topical cream that enhances the local immune response against BCCs).[24,25] Histologic evaluations of excised BCCs reveal that 50% provide evidence of at least partial regression. The immunoreactivity observed in BCCs and the surrounding stroma reflects an anti–tumor-specific immune response.[22]

Immunosuppressive treatments clearly increase BCC incidence. Organ transplant recipients have a 10-fold risk compared with the general population.[26] However, even much milder alterations in cell-mediated immunity can be consequential. For example, oral glucocorticoid therapy boosts BCC incidence, likely through decreased immunosurveillance.[27,28]

Chronic stressors can be a powerful immunomodulator during critical developmental periods, setting the stage for future alterations in skin cancer tumors. Mice that had been subjected to restraint stress subsequently developed UV-induced squamous cell carcinoma more rapidly than nonstressed control mice.[29] Furthermore, stressed mice also had a poorer immune response as assessed by messenger RNA (mRNA) immune markers in their tumors compared with controls. Indeed, even well after the stressor ended, the tumors of stressed mice did not regress like those of controls, suggesting that stressors early in development can continue to influence the immune response long after stress exposure.

Early stressful experiences combined with subsequent stress may be particularly detrimental. Seligman and Visintainer[30] exposed young rats to inescapable, escapable, or no shock conditions. When these rats reached adulthood, they were injected with cancer cells and exposed to 1 of the 3 shock conditions again. Rats exposed to inescapable shock when young (ie, an early environmental stressor) were more likely to develop tumors if also exposed to either shock condition as adults. However, rats that did not experience inescapable shock when they were young were not more likely to develop a tumor when exposed to shock as adults. These data suggest early life stressors may alter the immune response to subsequent stressors, thus decreasing antitumor defenses.

Parental emotional maltreatment is a common stressor in childhood. Maltreatment in childhood has been associated with atypical cortisol production throughout the day.[31,32] In adults, troubled early parent-child relationships have been linked to more pronounced stress-induced glucocorticoid production.[33,34] Compared with those who had healthy parent-child relationships, those who had adverse parent-child relationships are more likely to have emotional difficulties when they encounter subsequent stressors.[35]

Accordingly, this study addressed how parental emotional maltreatment and subsequent stressors might affect the BCC tumor environment. Assessment of the BCC tumor environment included 4 mRNA markers (ie, CD25, CD3ε, ICAM-1, and CD68) that have been linked to BCC tumor progression and regression. The BCC tumor biopsy specimens were taken from excised tissue. We hypothesized that childhood parental emotional maltreatment would be associated with a poorer local immune response to a BCC tumor if accompanied by a recent life stressor.

METHODS

STUDY PARTICIPANTS

Patients who had a newly diagnosed, histologically verified BCC received a letter from their treating dermatologist that described the study. Disqualifying health problems included immunosuppressive therapies or immunologic treatments for other medical conditions, another cancer diagnosed within the past 5 years (except for a prior BCC), or any history of squamous cell carcinoma or melanoma. We assessed childhood experiences and mRNA immune markers associated with BCC tumor progression and regression in 91 participants who had at least 1 prior BCC tumor. We chose to study individuals who previously had a BCC tumor because we wanted to know what sets the stage for subsequent BCC tumors that develop within 3 years in almost half of the people after their BCC.[20] The presence of the first tumor indicates that people already had enough sun exposure to get a BCC tumor and met their personal age threshold to start developing them. Accordingly, by studying individuals who had a history, we had a stronger basis for investigating psychosocial influences. This study was approved by the local institutional review board, and participants provided written informed consent.

RNA EXTRACTION AND COMPLEMENTARY DNA SYNTHESIS

We examined the expression of the following 4 mRNA markers: CD25 (the α chain of the IL-2 receptor expressed on activated T cells and B cells), CD3ε (a T-cell receptor marker), ICAM-1 (a cell surface glycoprotein on endothelial cells and immune cells), and CD68 (a marker for monocytes and macrophages) in BCC tumor tissue. The mRNA markers encode for proteins that are expressed on various immune cells; CD25 is the α chain of the IL-2 receptor expressed on activated T cells and B cells, CD3ε is part of the T-cell receptor–CD3 complex that has an important role in signal transduction after antigen recognition by the T cell, ICAM-1 is a cell surface glycoprotein on endothelial cells and immune cells that functions in the endothelial transmigration of immune cells, and CD68 is a hematopoietic differentiation marker of the monocyte and macrophage lineage.

Four 10-μm-thick sections obtained from each paraffin-embedded diagnostic biopsy specimen were immediately deparaffinized with xylene followed by hydration through graded ethanol washes. The tissue was then centrifuged and digested with 100 μL of digestion buffer (0.01M Tris, pH 7.8, 0.005M EDTA, and 0.5% sodium dodecyl sulfate) plus 100 μL of 20 mg/mL of proteinase K for 24 hours at 55°C with agitation. Total RNA was extracted by adding 800 μL of Trizol Reagent (Life Technologies) with 200 μg/mL of glycogen as a carrier. Total RNA was precipitated with 650 μL of 100% isopropanol at –40°C overnight then centrifuged at maximum speed at room temperature. The pellets were washed twice with 75% ice-cold ethanol. The RNA pellet was resuspended in nuclease-free water and quantified using a Nanodrop spectrophotometer. Total RNA (1 μg) was treated with DNase I (Life Technologies), followed by complementary DNA (cDNA) synthesis using Superscript

III RNase H- reverse transcriptase (Life Technologies). The cDNA was stored at –80°C until used for real-time polymerase chain reaction (PCR).

REAL-TIME PCR

TaqMan Gene Expression Assays (Applied Biosystems) were used for internal positive controls and the genes of interest. Using the Taqman Human Endogenous Control Plates (Applied Biosystems) and the GeNorm software (http://medgen.ugent.be/~jvdesomp/genorm/), we selected the following as best-fit internal positive controls for this study: glyceraldehyde-3-phosphate-dehydrogenase (GAPDH; assay No. 4326317E) and ribosomal protein, large, P0 (RPLP0; assay No. 4326314E). The expression of CD3ε (assay No. Hs99999153_m1), CD25 (assay No. 4328847F), CD68 (assay No. Hs00154355_m1), and ICAM-1 (assay No. Hs99999152_m1) mRNAs were normalized to the geometric mean of the cycle times for GAPDH and RPLP0. TaqMan Gene Expression Assay reagents do not detect genomic DNA sequences; therefore, these are specific to mRNA. The mRNA levels among samples were compared using relative real-time PCR with TaqMan fluorogenic probes, TaqMan PCR Reagent Kit, and 7300 Real-Time PCR System (Applied Biosystems). Because the complete study involved running samples in several 96-well plates, 1 cDNA sample from leukocytes previously characterized to express the genes of interest was also included in all the PCR runs to serve as the plate control for normalization. All the genes of interest were first normalized to the internal positive control and then normalized to the plate control, and the relative expression of mRNA species was calculated using the comparative cycle time method as described by the manufacturer.[36]

PSYCHOLOGICAL AND HEALTH-RELATED MEASURES

Detailed life event interviews were conducted to assess severe life events in the past year. The Life Events and Difficulty Schedule (LEDS) interview assesses the occurrence of more than 200 stressful events, with a goal of understanding the environmental stressors, while avoiding some of the biases that could occur from emotional status or coping resources.[37] When events are identified, interviewers gather data about a set of contextual factors that might intensify the meaning and implications of the event. For example, loss of employment is likely more stressful for someone who is already in debt and the sole family provider than one who has alternate sources of income. The LEDS has been widely used in psychiatric research, and severe life events predict the occurrence of psychiatric disorders, particularly depression. There are also documented links between the LEDS and illnesses.[38] For example, life stressors assessed by the LEDS were linked to increased cold susceptibility.[39]

Data gathered during interviews were presented to a set of raters who were masked to the participant's emotional or subjective reaction to the life stressor, Structured Clinical Interview for *DSM-IV* (SCID) data, child maltreatment scores, BCC mRNA levels, and participant's health. Raters (trained by S.L.J.) judged the severity of each life event on a 5-point scale, ranging from 1 (marked negativity) to 5 (little or no negativity) using the Bedford College dictionaries, which provide example ratings for more than 1000 life events occurring in different life contexts. They also rated whether events might be related to BCC status (eg, medical complications, lifestyle changes, or other ways in which the cancer diagnosis may have provoked the stressor). Any discrepancies were resolved through group discussion and consensus ratings. Interrater reliability was evaluated each month and was sustained at a level above intraclass correlations of 0.80 throughout the study. Inconsistencies across raters were reviewed, and ongoing training was conducted to ensure that raters followed guidelines carefully. Our study focused on the presence of at least 1 severe life event (as defined by severity ratings of 1 or 2) that was independent of the BCC and other illnesses. Although severe events can differ in individuals, the most common severe life events include the loss of a core confidant relationship, death of a family member, marital separation or divorce, or the loss of employment for the primary wage earner in the family. Because our goal was to document that environmental stressors can predict changes in disease status, we focused on events that were not related to illness to ensure that we were capturing stressors that were unrelated to an underlying biological vulnerability.

Although the LEDS takes approximately 10 hours for interviews, transcribing, and rating, the instrument's well-documented validity suggests that this care is warranted. It has significantly higher reliability and validity compared with self-report measures.[37,38,40,41]

The depression module of the nonpatient version of the SCID (SCID-NP) was administered by clinically trained interviewers to make relatively rapid and valid *DSM-IV* diagnoses.[42] Interrater reliability for SCID-NP diagnoses was calculated using randomly selected audiotapes for 20% of the participants. There was greater than 85% agreement for each of the 5 diagnoses tested, with the Cohen κ ranging from 0.64 to 0.69. This substantial interrater agreement was confirmed with the McNemar test for marginal proportions ($P > .99$ for all diagnoses).

A history of parental emotional maltreatment was assessed with the antipathy and neglect subscales of the Childhood Experience of Care and Abuse Questionnaire (CECA.Q),[43] which examines emotional maltreatment by parents from birth to 17 years of age. All items from the questionnaire were derived from the well-validated CECA interview.[44] On a 5-point Likert-type scale ranging from "yes, definitely" to "no, not at all," the antipathy (mother and father) subscale assessed hostile and rejecting parenting (eg, "She was very critical of me" and "He made me feel unwanted"), and the neglect subscale assessed the extent to which parents provided material or emotional support for their children (eg, "He was concerned about my whereabouts" and "She tried to make me feel better when I was upset"). A 1-U increase or decrease in maltreatment reflects a unit increase on the 1- to 5-point scale. The neglect subscale was highly correlated with the antipathy subscale for both parents (mothers: $r = 0.72$, $P < .001$; fathers: $r = 0.77$, $P < .001$). In accord with prior work, we combined both scales[45]; maternal antipathy and neglect and paternal antipathy and neglect scores were averaged to create an overall mother emotional maltreatment composite and father emotional maltreatment composite.

The CECA.Q possesses good test-retest reliability and alternate forms of reliability when compared with the CECA interview in both community and clinical populations.[46] Furthermore, the antipathy and neglect subscales of the CECA.Q converge with other popular measures of childhood adversity, including the Parental Bonding Instrument,[47] suggesting this measure possesses good convergent validity. The questionnaire instructs respondents to fill out the CECA.Q in reference to the mother and father figure who they were "with the longest" or the one they found "most difficult to live with." Ninety-four percent of participants filled out the questionnaire in reference to their biological mother, and 93% responded in reference to their biological father.

The Center for Epidemiological Studies Depression Scale (CES-D) provided data on current depressive symptoms.[48,49] Studies[49] have shown acceptable test-retest reliability and excellent construct validity. It has been widely used in cancer studies.[50]

The Pittsburgh Sleep Quality Index provided data on sleep quality and sleep disturbances.[51]

Table 1. Characteristics of the 91 Study Participants

Characteristic	Finding
Female sex, No. (%)	43 (47)
White race, No. (%)	91 (100)
Educational level, No. (%)	
High school or less	19 (21)
Some college	26 (29)
College degree	46 (51)
Marital status, No. (%)	
Single	7 (8)
Married	69 (76)
Common law	2 (2)
Divorced	9 (10)
Widowed	4 (4)
Age, y	
Mean (SD)	58.2 (13.5)
Range	23-92
No. of LEDS events, No. (%)	
0	70 (77)
1	17 (19)
≥2	4 (4)
Time from most recent LEDS event to biopsy, mo (n = 21)	
Mean (SD)	5.5 (3.2)
Range	0.1-11
History of major depression, No. (%)	30 (33)
CES-D score	
Mean (SD)	7.8 (9.0)
Median (IQR)	6 (2-9)
Range	0-49
Pittsburgh Sleep Quality index	
Mean (SD)	4.9 (2.7)
Range	0-15
Any comorbid conditions, No. (%)	65 (71)
Current smoker, No. (%)	10 (11)
Consume alcohol, No. (%)	46 (51)
Emotional maltreatment according to the CECA.Q	
Mother	
Mean (SD)	12.6 (5.5)
Range	8-31.5
Father	
Mean (SD)	14.4 (6.5)
Range	8-31
Messenger RNA Levels	
CD25	
Median (IQR)	38 (12-103)
Range	2.5-1284
CD3ε	
Median (IQR)	0.23 (0.10-0.56)
Range	0.020-16
ICAM-1	
Median (IQR)	0.24 (0.13-0.50)
Range	0.015-3.5
CD68	
Median (IQR)	1.5 (0.56-3.6)
Range	0.11-38
BCC tumor type, No. (%)	
Nodular	27 (30)
Superficial	15 (16)
Mixed type	49 (54)
BCC site, No. (%)	
Head and neck	50 (55)
Trunk	17 (19)
Upper limbs	15 (16)
Lower limbs	3 (3)
Multisite	6 (7)
Skin type (burning), No. (%)	
Always burn	11 (12)
Usually burn	17 (19)
Burn moderately	31 (34)
Burn minimally	21 (23)
Rarely or never burn	11 (12)
No. of sunburns before 19 years of age, No. (%)	
0	4 (4)
1-9	44 (48)
10-19	23 (25)
≥20	19 (21)
Unknown	1 (1)

Abbreviations: BCC, basal cell carcinoma; CECA.Q, Childhood Experience of Care and Abuse Questionnaire; CES-D, Center for Epidemiological Studies Depression Scale; ICAM-1, intercellular adhesion molecule 1; IQR, interquartile range; LEDS, Life Events and Difficulties Schedule.

The Older Adults Resources Survey Multidimensional Functional Assessment Questionnaire assessed underlying diseases and associated medications.[52] Several studies have found excellent agreement between self-reports and hospital or physician records for specific conditions, including myocardial infarction, stroke, and diabetes mellitus.[53,54]

STATISTICAL ANALYSIS

The mRNA markers (levels of CD25, CD3ε, ICAM-1, and CD68) were highly correlated, with pairwise Spearman correlation coefficients ranging from 0.78 to 0.91 and a Cronbach α of 0.95 (using log-transformed values). Thus, a single composite mRNA index was created for each study participant using *z* scores. For each participant, the *z* scores for each (base 10) log-transformed mRNA marker were calculated, and these 4 *z* scores were averaged to produce the summary construct. These cell surface markers operate together in vivo; this combined index reflects this coordinated immune response to the BCC tumor. We used this mean mRNA *z* score as the primary outcome of interest. Secondary analyses used depressive symptoms (CES-D) scores as the outcome.

Linear regression analyses were conducted to evaluate associations among parental emotional maltreatment, the experience of severe life events, and each outcome. The LEDS life events variable was dichotomized at 0 vs 1 or more in the past year. Adjusted models controlled for age and sex. Models for the mRNA *z* score index additionally controlled for smoking status, alcohol consumption, comorbid conditions, sleep quality (Pittsburgh Sleep Quality index), and BCC tumor type. Residual plots were examined for all models, and when the normality assumption was found to have failed, outcomes were log-transformed. The α was set to .05, and 2-sided tests were conducted. All analyses were performed with SAS statistical software, version 9.1 (SAS Institute, Inc).

RESULTS

Participant sample characteristics are summarized in **Table 1**. There were 48 men and 43 women in the sample, most of whom had at least some college education (72 [79%]). This cancer occurs among those with fair skin, and all participants self-described themselves as white.[55] The mean (SD) age at interview was 58.2 (13.5) years. The 91 participants were generally healthy with few comorbid conditions: asthma (5 [5%]), emphysema (2 [2%]), heart disease (8 [9%]), hypertension (27 [30%]), kidney disease (2 [2%]), liver disease (1 [1%]), stroke (2 [2%]), and thyroid disease (4 [4%]). Comorbid conditions did not include psychiatric conditions. Neither paternal nor maternal emotional mal-

Table 2. Association of Maternal Emotional Maltreatment and LEDS Events With Mean Messenger RNA *z* Score[a]

	Unadjusted Model (R^2 = 0.08)		Adjusted Model (R^2 = 0.28)	
Variable	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Maternal emotional maltreatment	0.0077 (–0.033 to 0.048)	.71	0.020 (–0.024 to 0.065)	.37
Any LEDS events	0.98 (–0.099 to 2.1)	.07	1.1 (0.044 to 2.1)	.04
Maternal emotional maltreatment × any LEDS events	–0.10 (–0.18 to –0.019)	.02	–0.11 (–0.18 to –0.028)	.009
Paternal emotional maltreatment			–0.013 (–0.046 to 0.021)	.45
Age, y			–0.0019 (–0.017 to 0.013)	.81
Female (reference: male)			–0.45 (–0.86 to –0.038)	.03
Comorbid conditions			–0.060 (–0.28 to 0.16)	.59
Smoker (reference: nonsmoker			–0.037 (–0.63 to 0.56)	.90
Drinks alcohol (reference: nondrinker)			0.037 (–0.35 to 0.42)	.85
Pittsburgh Sleep Quality index			0.034 (–0.036 to 0.11)	.34
Tumor type (reference: mixed)				
Nodular			–0.81 (–1.2 to –0.40)	<.001
Superficial			–0.38 (–0.90 to 0.14)	.15

Abbreviation: LEDS, Life Events and Difficulties Schedule.
[a]Results from linear regression models (91 patients).

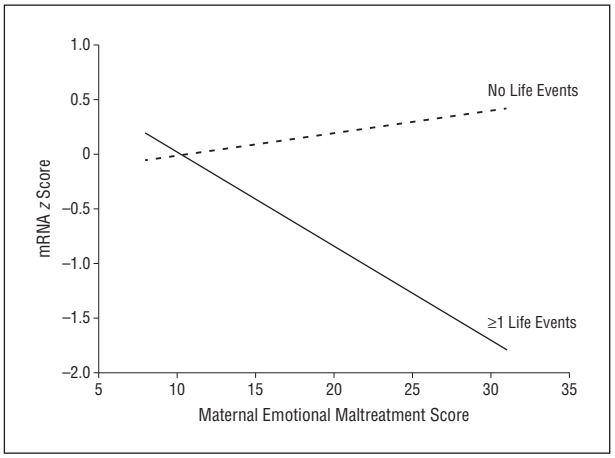

Figure. Interaction plot illustrating the association among maternal emotional maltreatment, severe life events, and composite messenger RNA (mRNA) *z* score from the adjusted model in Table 2. Values of all other variables in the model are set to their sample means.

treatment was associated with age (mothers: r=0.14, P=.20, fathers: r=0.17, P=.11). Parental maltreatment was not associated with the experience of any severe life events (mothers: r=0.10, P=.35, fathers: r=0.17, P=.10).

Table 2 summarizes the association of maternal emotional maltreatment and life events with the mean mRNA *z* score. In the unadjusted model, a significant interaction was found between maternal emotional maltreatment and the experience of any severe life events, and this interaction persisted in the adjusted model (unadjusted P=.02, adjusted P=.009). The experience of severe life events led to a negative association between maternal emotional maltreatment and mRNA *z* score. In the adjusted model, a 1-U increase in maternal emotional maltreatment was not significantly associated with mRNA *z* score for participants with no life events (B=0.020; 95% CI, –0.024 to 0.065; P=.37). However, for participants with 1 or more severe life events, a 1-U increase in maternal emotional maltreatment score led to a 0.086-point decrease in mRNA *z* score (95% CI, –0.15 to –0.017; P=.02). This interaction is illustrated in the **Figure**.

Table 3 summarizes a similar interaction between paternal emotional maltreatment and life events in predicting mRNA *z* score (unadjusted P=.02, adjusted P=.03). In the adjusted model, a 1-U increase in paternal emotional maltreatment was significantly associated with a 0.063-point decrease in mRNA *z* score (95% CI, –0.12 to –0.010; P=.02) for participants who had experienced any severe life events. Participants who had not experienced any life events did not have a significant relationship between paternal emotional maltreatment and mRNA *z* score (B=0.009; 95% CI, –0.031 to 0.050; P=.65).

Additional analyses evaluated the effect of removing paternal emotional maltreatment from the adjusted model in Table 2 and maternal emotional maltreatment from the adjusted model in Table 3 because paternal and maternal emotional maltreatment were moderately correlated (r=0.42, P<.001). Removing paternal emotional maltreatment had negligible effects on estimates for maternal emotional maltreatment and vice versa in both mRNA *z* score models. We also considered an interaction between maternal and paternal emotional maltreatment to assess any added effect when both parents emotionally maltreated their children; results were nonsignificant (P=.34).

Post hoc analyses were performed by repeating the models in Tables 2 and 3 using each of the mRNA markers (log-transformed) as the outcome (8 total separate adjusted regression models). Results matched those of the composite models and were consistent across all mRNA variables. The emotional maltreatment by LEDS interaction significantly predicted each mRNA variable in all but 1 model; the only nonsignificant interaction was in the model using paternal emotional maltreatment predicting CD3ε, and the effect was in the expected direction (P=.13).

A separate linear regression model to assess the association among parental emotional maltreatment, severe life events, and CES-D is presented in **Table 4**. The in-

Table 3. Association of Paternal Emotional Maltreatment and LEDS Events With Mean Messenger RNA *z* Score[a]

	Unadjusted Model (R^2 = 0.08)		Adjusted Model (R^2 = 0.26)	
Variable	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Paternal emotional maltreatment	0.010 (–0.027 to 0.048)	.59	0.0094 (–0.031 to 0.050)	.65
Any LEDS events	1.1 (–0.073 to 2.2)	.07	1.0 (–0.14 to 2.2)	.08
Paternal emotional maltreatment × any LEDS events	–0.076 (–0.14 to –0.011)	.02	–0.073 (–0.14 to –0.0086)	.03
Maternal emotional maltreatment			–0.010 (–0.049 to 0.030)	.63
Age, y			–0.0025 (–0.018 to 0.013)	.75
Female (reference: male)			–0.39 (–0.80 to 0.023)	.06
Comorbid conditions			–0.0090 (–0.23 to 0.21)	.94
Smoker (reference: nonsmoker)			–0.090 (–0.70 to 0.52)	.77
Drinks alcohol (reference: nondrinker)			–0.076 (–0.46 to 0.31)	.69
Pittsburgh Sleep Quality Index			0.023 (–0.049 to 0.10)	.52
Tumor type (reference: mixed)				
Nodular			–0.80 (–1.2 to –0.38)	<.001
Superficial			–0.42 (–0.94 to 0.11)	.12

Abbreviation: LEDS, Life Events and Difficulties Schedule.
[a] Results from linear regression models (91 patients).

teraction between parental emotional maltreatment and life events predicting depressive symptoms was not significant (P=.35 for maternal emotional maltreatment and P=.41 for paternal emotional maltreatment), so we eliminated the interaction term from Table 4 as is the standard convention.[56] Paternal emotional maltreatment was positively associated with depressive symptoms. A 1-U increase in paternal emotional maltreatment was associated with a 4.0% increase in the CES-D score (P=.03). Neither maternal emotional maltreatment nor severe life events were significantly associated with CES-D, although slope estimates were in the expected direction. A history of major depression (as assessed by the SCID) was not associated with maternal emotional maltreatment (Wilcoxon rank sum, P=.80), paternal emotional maltreatment (Wilcoxon rank sum, P=.08), or severe life events (χ^2 test, P=.27).

The CES-D scores were not associated with mRNA *z* score in unadjusted or adjusted models and did not mediate the effects of parental emotional maltreatment on mRNA *z* score (results not shown). The same conclusions held when we looked at the effect of a history of major depression (as assessed by the SCID) in place of CES-D. Adding CES-D or history of major depression as a predictor did not change the point estimates or significance of paternal or maternal emotional maltreatment or life events or their interaction in the models presented in Tables 2 and 3. In the CES-D model (Table 4), removing maternal emotional maltreatment resulted in a small (4%) increase in the point estimate for paternal emotional maltreatment, with a subsequent decrease in the *P* value to .01. Adding sunburn history, skin type, and/or time since life events as predictors did not change the point estimates or significance levels of our results presented in Tables 2 and 3. If we included illness-related severe events, only 2 additional people were added to the severe life event group; all of the analyses remained the same (ie, point estimates did not change substantially, and significance levels were identical). The number of previous BCCs did not predict differences in mRNA levels or alter our findings. Finally, the pattern of results remained the same when the antipathy and neglect subscales of the CECA.Q were assessed independently.

Table 4. Association of Maternal and Paternal Emotional Maltreatment and LEDS Events With Depressive Symptoms (CES-D[a])

	Adjusted Model (R^2 = 0.15)	
Variable	Estimate (95% CI)	*P* Value
Age, y	–0.005 (–0.020 to 0.010)	.51
Female (reference: male)	0.25 (–0.16 to 0.66)	.24
Any LEDS events	0.32 (–0.16 to 0.79)	.19
Maternal emotional maltreatment	0.004 (–0.037 to 0.044)	.85
Paternal emotional maltreatment	0.039 (0.0043 to 0.074)	.03

Abbreviations: CES-D, Center for Epidemiological Studies Depression Scale; LEDS, Life Events and Difficulties Schedule.
[a] Outcome (CES-D) is natural log transformed. Results from a linear regression model (91 patients).

COMMENT

Our results show that among BCC patients who experienced a severe stressor in the past year, those who were emotionally maltreated by their mothers or fathers as children were more likely to have poorer immune responses as reflected in lower levels of mRNA for CD25, CD3ε, ICAM-1, and CD68 to their BCC tumors. Being emotionally maltreated by one's father was also linked to higher depressive symptoms. However, depressive symptoms and a history of depression were not directly linked to the BCC immune responses related to the BCC tumor. Women had a poorer immune response to the BCC tumor than men; most of the prior literature on BCC immune responses has not analyzed responses by sex, so it is unclear whether this is typical or not.

The immune system plays a prominent role in response to BCC tumors because they are immunogenic, unlike many other common cancers that do not show the same responsiveness to the immune system.[22] Studies addressing control of BCC tumor progression show that in-

flammatory cells in the peritumoral milieu and those that infiltrate BCC tumors have important roles.[23,57,58] Although key risk factors for a person's first BCC include childhood sun exposure, fair skin, and male sex, subsequent tumors are not reliably related to these variables.[20,21] Psychological stress may play an important role in the tumor environment for this immunogenic tumor and have important implications for subsequent BCC tumors. Future studies should further investigate the clinical implication of the current findings.

Mechanistically, troubled parent-child relationships can alter the set point for the stress response system. Individuals who had adverse childhood relationships are more physiologically reactive to stress as adults compared with those who did not.[59] As described previously, early life adversity has been linked to subsequent dysregulated immune function in adults and physiologic responsiveness to subsequent stressors.[11-14,60]

We examined mRNAs encoding for proteins that are expressed on various immune cells and have been implicated in their function; mRNAs carry the information that specify the properties of the protein end product. The expression of mRNAs for CD3ε, CD68, CD25, and ICAM-1 indicates a coordinated immune response to the BCC tumor. In general, BCC tumor tissue has higher levels of mRNA immune markers than healthy tissue because the immune system is responding to the tumor. The presence of these markers in BCC tumors is suggestive of infiltration of immune cells as part of the antitumor immune response.[23-25,57,61,62]

This study extends animal work demonstrating that stress, especially early in life, can affect tumor growth and progression.[30] Our findings complement work demonstrating that early life stress increases vulnerability to tumor development when exposed to an additional stressor in adulthood.[30]

Our findings also complement other studies[63,64] that have addressed the relationship between psychosocial factors and immune markers within the tumor environment. Patients with ovarian cancer who were more distressed had poorer natural killer cell activity in tumor-infiltrating lymphocytes than those who were less distressed.[63,64] Furthermore, those who had more social support had greater natural killer cell activity in tumor-infiltrating lymphocytes than those who had less support. To our knowledge, the current study is the first to show that early life stressors can also influence the tumor environment in humans.

Our work may have broader implications for other cancers. In a large, prospective study[65] with more than 1 million participants, those with nonmalignant skin cancers were 20% to 30% more likely to die of other noncutaneous cancers; the relative risk for mortality from other cancers was 1.30 in men and 1.26 in women. A recent meta-analysis[66] reported that individuals who were more stress reactive were at greater risk for cancer mortality than those who were not. Accordingly, BCCs may have some prognostic value for broader cancer risks.

These findings could also be relevant to recent work linking child maltreatment with cancer incidence. One study demonstrated a dose-response relationship between the number of exposures to abuse or household dysfunction during childhood and cancer incidence.[16] In other work, those who were physically abused as children had 49% higher odds of having a cancer diagnosis than those who were not abused.[67] The findings remained after adjusting for health behaviors, such as smoking and exercise; immune dysregulation may have contributed to this link.[67]

One major strength of this study was the use of the LEDS to assess life events. The LEDS allowed us to exclude life events that were related to underlying medical issues. Furthermore, because the LEDS uses objective ratings of stress severity, biases related to depressive symptoms do not influence people's ratings of their life stress. Accordingly, the LEDS allowed us to assess links between severe stressors and immune function with control over biased reporting of stress related to depressive symptoms and poor health.

Despite the potential importance of understanding how early adverse experiences influence cancer risk, several limitations should be acknowledged. Our participants could have been biased when reporting the degree to which their parents emotionally maltreated them as children. However, adults generally underreport rather than overreport childhood abuse and neglect.[68] In addition, many other forms of child adversity that could also affect immune function have not been assessed in the current study, such as low socioeconomic status.[69] Future work should take these factors into account as well. Another limitation is our exclusive focus on BCC tumors. We chose this disease because of the known immunogenic properties of BCC tumors, but future work assessing other types of tumors will be important to generalize our findings to cancer more broadly. Finally, our sample was exclusively white, which is not surprising given the nature of the disease.

Basal cell carcinoma is a substantial public health concern; it is highly prevalent and carries risks of scarring and disfigurement.[20] Furthermore, it may be prognostic for other cancers. A better understanding of the factors that contribute to BCC incidence and reoccurrence is clinically relevant. Troubled early parental experiences are linked to greater stress reactivity in adulthood and poorer immune regulation. This is the first study, to our knowledge, to show that troubled early parental experiences, in combination with a severe life event in the past year, predict local immune responses to a BCC tumor. These data complement and expand increasing evidence that the consequences of early parental experiences extend well beyond childhood.

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