What New Gene Expression Research Means for Skin Cancer Management

Ongoing developments in the field of gene expression may finally be leading to clinical tools.

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Over the last decade or more, research has uncovered numerous genes that seem to directly or indirectly mediate the genesis and progression of non-melanoma skin cancers (NMSC). Recent research suggests that these findings may finally be leading to clinically relevant screenings or interventions.

Genotyping for At-Risk Patients

CTLA4 (Cytotoxic T-Lymphocyte Antigen 4) has been implicated in various autoimmune diseases as well as certain cancers. (See sidebar) CTLA4 has been associated with UV-induced tolerance and induction of (NMSC) and melanoma. Anti-CTLA4 antibodies are currently under investigation for treatment of melanoma in clinical trials. Recent developments with Anti-CTLA4 have turned to NMSC.

Researchers have confirmed that a single nucleotide polymorphism (SNP) in the CTLA-4 coding region (49A > G) is associated with human cancer; but this is the opposite allele for susceptibility to autoimmune diseases. Another set of researchers has turned their attention to the SNP CT60, which has been closely associated with autoimmune disease. They hypothesized that increased risk of autoimmune disease mediated by CT60GG actually decreases risk of SCC and BCC. It is feasible that constant immune activation (which can lead to autoimmunity) would help to “micro manage” the damage induced by the sun on a regular basis. Furthermore, autoimmunity may counteract the sun’s inhibition of immune response. This model would appear to be particularly relevant given the hypothesis that chronic sun exposure leads to NMSC, versus acute exposure leading to melanoma (thus, the immune system is not chronically activated).

The researchers undertook a population-based case-control study of Caucasians in New Hampshire (849 controls, 930 BCC, and 713 SCC) to test their hypothesis. After controlling for age, sex, lifetime number of severe sunburns, and skin type, they determined that the CTLA4 CT60 GG genotype was associated with decreased odds for BCC (OR: 0.7; 95% confidence interval: 0.5-0.9) and SCC (OR: 0.7; 95% CI: 0.5-1.0). The decreased odds for BCC were apparent among those with a higher lifetime number of severe sunburns. The authors conclude that genetic variation at the CTLA4 locus may be etiologically important in NMSC.

If further research confirms the association of SNP CT60, then genetic profiling of patients could become part of standard practice. Genotyping is possible via simple blood tests. Individuals with greater risk for NMSC can be urged to take more aggressive measures to protect against UV skin damage and be vigilant for new and changing skin lesions.

Gene-Inhibiting Therapy for BCC

Activation of the Hedgehog signaling pathway has been implicated in a variety of solid tumors and blood cancers, and hedgehog pathway inhibitors are
Mutations of the patched homologue 1 (PTCH1, See Sidebar) and smoothened homologue (SMO) genes that encode the hedgehog pathway have been associated with BCC. SMO homologue genes are shown to promote growth of BCCs, while PTCH usually inhibits SMO. Therefore, SMO homologue or mutation in PTCH (so that it does not inhibit SMO) are associated with BCC. Recognizing these relationships prompted researchers to investigate a small-molecule inhibitor of SMO as a treatment for locally advanced or metastatic BCC. It would, in a sense, function like PTCH.

Thirty-three patients with metastatic or locally advanced BCC were randomized to receive oral GDC-0449 150mg/day (17 patients), 270mg/day (15 patients), and 540mg/day (one patient) for a median duration of 9.8 months. Of the 33 patients, 18 had an objective response to GDC-0449: seven according to assessment on imaging, 11 on physical examination (one patient rated on both). Two patients had a complete response and 16 had a partial response. Of the remaining patients, only four had progression of disease, and 15 patients remained stable. Fatigue, hyponatremia, muscle spasm, or atrial fibrillation (one case) deemed possibly associated with treatment were reported by six patients. One incident of asymptomatic hyponatremia was judged to be unrelated to GDC-0449. The authors noted evidence of hedgehog signaling in tumors that responded to treatment.

Given these positive results, further study of oral GDC-0449 in BCC and other malignancies is certain. If similar positive results are found, dermatologists may one day see an effective oral treatment for BCC. There is some speculation that a topical formulation of GDC-0449 could be developed. Such a formulation would allow targeted therapy theoretically with reduced risk of systemic side effects.

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2. Ribas A. Anti-CTLA4 Antibody Clinical Trials in Melanoma. Update Cancer Ther. 2007 Sep;2(3):133-139.