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Genetic Variations in Squamous Cell Carcinoma of the Oropharynx

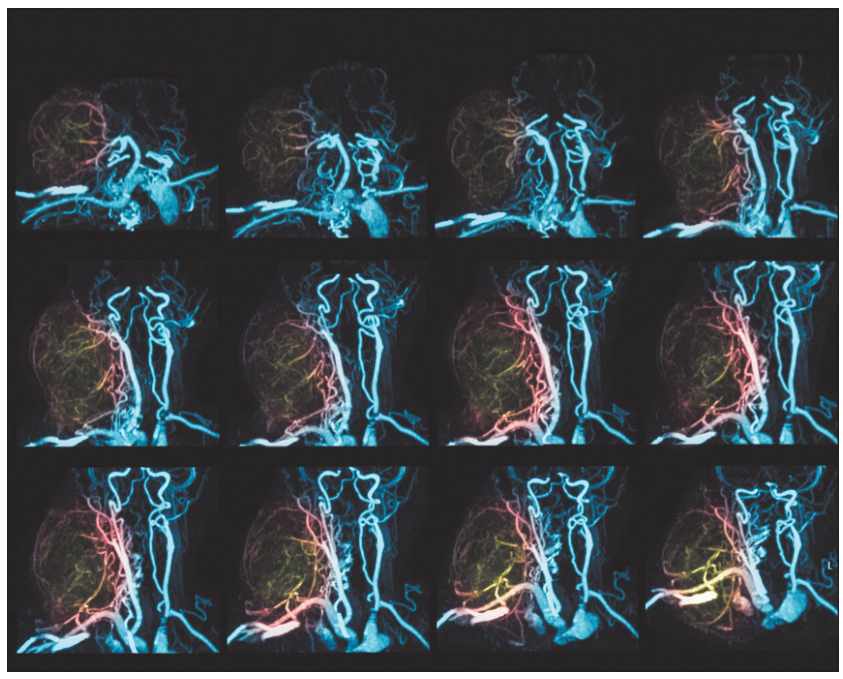
BY RICHARD SIMONEAUX

There are a number of cancers of the head and neck, one of which is squamous cell carcinoma of the oropharynx (SCCOP). Although in the past, the use of alcohol and tobacco products have been leading risk factors for SCCOP, an increasing number of patients have developed this disease as a result of their exposure to HPV. One of the most common forms of the virus which is deemed high-risk, or capable of causing cancer in men and women, is HPV16. Although cervical cancer is most commonly associated with HPV, this virus can cause cancers in other mucous membranes, such as the vagina, vulva, anus, or the mouth and throat (including the oropharynx).

CME Article

Transforming growth factor-β1 (TGF-β1) is a polypeptide cytokine that plays crucial roles in inflammation and the immune system.

Continued on page 10



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Investigating Mechanisms to Better Understand Immune Response

BY VALERIE NEFF NEWITT

Randy Sweis, MD, spends hours upon hours in his lab at the University of Chicago trying to unravel mechanisms of resistance to cancer immunotherapies and develop strategies to modulate the tumor microenvironment, with a goal of improving anti-tumor immune responses.

But that is only half of the professional load he has undertaken. Sweis is also a caring, patient-facing clinician who has created an impressive symbiotic relationship between the lab and his clinical practice. He translates his laboratory findings to patient care by asserting his expertise in drug development and early-phase clinical trials.

The University of Chicago physician-scientist reports weekly to his clinical practice where he treats patients with genitourinary malignancies including bladder, kidney, prostate, and testicular

Continued on page 11

T-Cell Biomarker Predicts CLL Patients' Response to CAR T-Cell Therapy

Penn Medicine researchers in Philadelphia may have found the reason why some patients with advanced chronic lymphocytic leukemia (CLL) don't respond to chimeric antigen receptor (CAR) T-cell therapy, and the answer is tied to how primed patients' immune systems are before the therapy is administered. While 80 percent of patients with advanced acute lymphoblastic leukemia (ALL) treated with the CAR T-cell therapy tisagenlecleucel have a dramatic response, only 26 percent of CLL patients respond to it in clinical trials.

A new study from the Abramson Cancer Center of the University of Pennsylvania shows that CLL patients possessing a subset of vital, healthier T cells prior to CAR T-cell therapy had a partial or complete clinical response to the treatment, while those lacking enough of those T cells did not respond. These healthier "early memory" T cells were marked by the expression of CD8 and CD27, as well as the absence of CD45RO. The findings show the potential to improve responses by enhancing a patient's immune cells with emerging cell manufacturing techniques before CAR T-cell therapy (*Nat Med* 2018; doi:10.1038/s41591-018-0010-1).

What's more, the team—which was led by senior author J. Joseph Melenhorst, PhD, and first author Joseph A. Fraietta, PhD, both faculty in the department of Pathology and Laboratory Medicine in Penn's Perelman School of Medicine and Penn's Center for Cellular Immunotherapies—also validated

Continued on page 18

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Genetic Variations in Squamous Cell Carcinoma of the Oropharynx

continued from page 1

Consequently, it is possible that variations in the gene that encodes TGF-β1 (*TGFB1*) could alter the manner in which SCCOP patients may respond to their disease.

To investigate this possibility, a team of clinicians at The University of Texas MD Anderson Cancer Center, Houston, including Guojun Li, MD, PhD, undertook a study that genotyped 564 incident SCCOP patients for three different polymorphisms of *TGFB1* to assess the effect that variation of that gene had on the overall (OS), disease-specific survival (DSS), and disease-free survival (DFS) in this patient subpopulation (*Clin Cancer Res* 2018; doi:10.1158/1078-0432.CCR-17-1904). The three polymorphisms evaluated in this study included *TGFB1* rs1800469, rs1800471, and rs1982073.

When asked to discuss the reasons for this trial, Li replied, "Although several studies have investigated the association between HPV and TGF-β1 expression levels in cervical cancer and assessed their influence on primary risk, few have evaluated their effects on survival." Concerning the results, he noted, "Patients with the *TGFB1* rs1982073 CT/CC polymorphism had statistically significantly better OS, DSS, and DFS compared with those with the corresponding common homozygous TT genotype.

"Furthermore, these genotypes were significantly associated with an approximately 5 times reduced risk of overall death, death owing to disease, and recurrence after multivariable adjustment. However, the tumor HPV status stratification data indicated that the significant effects of *TGFB1* rs1982073 polymorphism on survival were found among HPV16-positive SCCOP patients only."

Background

The epithelial tissue-based SCCOP is characterized by aggressive tumors that have high local recurrence rates as well as frequently having more than one primary tumor site. Although the frequency of SCCOP has remained fairly constant at about three cases per 200,000 people, an increasing number of these patients are now younger, often as a result of disease arising from HPV infection. In 2016, there were approximately 48,000 new cases of SCCOP and slightly more than 9,500 deaths from this disease. Despite the decrease in the overall incidence of head and neck cancers, there has been a slight uptick in the numbers of SCCOP cases.

Currently, the two main treatments for SCCOP consist of radiotherapy or the combination of chemoradiation. In patients having early-stage disease, the therapy of choice is often radiotherapy alone. However, for later-stage patients, chemoradiation is the preferred treatment modality.

"Specifically, studies have shown that although greater toxicity is observed with chemoradiation than with radiotherapy alone, both DFS and OS tend to be better with the concomitant therapy," Li noted. "In our practice, we often use cisplatin, taxol, and 5-fluorouracil as agents in the chemoradiation combination therapies."

TGF-β1

Regarding the specific polymorphisms, Li explained, "We chose to study the *TGFB1* polymorphisms rs1800469, rs1982073, and rs1800471 because these appear to affect TGF-β1. The first variant, *TGFB1* rs1800469, is located in the promoter region of the gene and is associated with differences in circulating TGF-β1 plasma levels. Prior studies showed that when cytosine is encoded, activator protein 1 (AP1) binds to it, resulting in the downregulation of *TGFB1*," Li added (*Hum Genet* 2006;120(4):461-469). Concerning the *TGFB1* rs1982073 variant, Li stated, "This polymorphism is located at codon 10 of exon 1 and results in a non-synonymous change from leucine to proline within the signal peptide sequence of TGF-β1. This region of the gene is responsible for directing TGF-β1 into the extracellular matrix and the wild type T allele has been associated with lowered secretion and serum levels of TGF-β1 compared with the variant C allele (*Exp Rev Anticancer Ther* 2004;4(4):649-661). "*TGFB1* rs1800471 is located at codon 25 in exon 1 and results in an arginine to proline change," Li noted regarding the third *TGFB1* variant.

"In addition, we previously have reported that *TGFB1* rs1982073 was significantly associated with HPV16-positive SCCOP tumors; however, no studies have investigated whether *TGFB1* polymorphisms are associated with survival of SCCOP patients, particularly HPV16-positive SCCOP patients. We hypothesized that TGF-β1 polymorphisms are associated with survival of SCCOP patients after radiation or chemoradiation," Li explained.

Study Methodology

From January 2000 to May 2013, 564 newly diagnosed incident SCCOP patients from The University of Texas MD Anderson Cancer Center were recruited to participate in an ongoing molecular epidemiology study. All participants had histologically confirmed disease and were untreated. Patients were not excluded from the study on the basis of age, cancer stage, ethnicity, histology, or sex. Upon enrollment, patients provided a blood sample (~30 mL) for *TGFB1* genotyping, as well as completed a questionnaire to provide demographic and risk factor data (e.g., smoking and alcohol status).

Both PCR and in situ hybridization methods were utilized to detect the presence of HPV16 in DNA material obtained from SCCOP patient-derived paraffin-embedded tumor samples. "For some SCCOP patients, tumor HPV16 status was determined by in situ hybridization and p16 immunohistochemical analysis from HPV data in the patient's clinical records, as the pathology laboratory at MD Anderson had begun classifying all SCCOP specimens as a matter of standard clinical practice," Li explained.

Clinical data, which were obtained at both initial presentation and throughout follow-up examinations, included the following: stage of the index tumor at presentation, site of the index tumor, and treatment. Dichotomization was done for both index cancer stage (early-stage (stage I or II disease) or late-stage (stage III or IV)) and treatment (radiotherapy alone or chemoradiation) parameters. Comorbidity classification was performed using a modified Kaplan-Feinstein index (Adult Comorbidity Evaluation 27), in which related comorbidities were categorized as none, mild, moderate, or severe.

Primary endpoints for the study included overall deaths, deaths due to disease, and recurrence. Differences in OS, DFS, and DSS among the SCCOP patients were determined. Time to recurrence was defined as the time between the end of treatment and the date of last follow-up or clinical detection of recurrent cancer (local, regional, or distant). Those patients who did not have disease recurrence or who were lost to follow-up were censored from the results. Survival criteria were defined as follows: OS—the time between first appointment and death from any cause or date of last follow-up; DSS—time between first appointment and death from disease or date of last follow-up. Participants who were alive at the end of

Continued on page 30

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Learning Objectives for This Month's CME Activity: After participating in this CME activity, readers should be better able to distinguish characteristics of cancers caused by HPV and analyze results of a trial that evaluated the effect on prognosis of 3 TGF-β1 polymorphisms for patients with SCCOP.

continued from page 10

the study period or lost to follow-up were censored for both OS and DSS calculations.

Result Findings

For the 564 patients included in this study, the median age at diagnosis was 55 years with a range of 28-82 years. Additionally, 491 (87.1%) were male; 518 (91.8%) had white, non-Hispanic ethnicity; and 528 (93.6%) had late-stage (III or IV) index cancer. Histories of smoking and alcohol use were noted in 284 (50.3%) and 377 (66.8%) patients, respectively. In terms of treatments, only 23.6 percent had radiotherapy alone while 76.4 percent had radiochemotherapy combination. During the course of this study, there were only 78 deaths from all causes;, however, only 44 were considered disease-related. Positive HPV tumor status was noted in 85 percent of the participants in this study.

When calculating HRs, these figures were adjusted for the following factors: age, sex, HPV status, treatment, comorbidity, smoking status, alcohol use. HR values for the *TGFB1* rs1982073 variant participants were determined utilizing data from the 170 patients having the TT genotype as the reference (i.e., HR defined as 1.0) for evaluating the 394 patients having the CT+CC variant genotypes. For CT+CC genotypes, the OS, DSS, and DFS data afforded HR values of 0.2 (95% CI: 0.1–0.5; p< 0.001), 0.2 (95% CI: 0.1–0.4; p< 0.001), and 0.2 (95% CI: 0.1–0.4; p< 0.001), respectively.

When stratification of data was performed using tumor HPV16 status, as before, data from the *TGFB1* rs1982073 variant participants with the TT genotype were utilized as the reference. For the participants with HPV16-positive tumors having the CT+CC variant genotypes (n=327), OS, DSS, and DFS data yielded HR values of 0.1 (95% CI: 0.1–0.3; p< 0.001), 0.1 (95% CI: 0.1–0.3; p< 0.001), and 0.2 (95% CI: 0.1–0.3; p< 0.001), respectively.

Correspondingly, for HPV16-negative CT+CC variant genotype participants (n=67), the OS, DSS, and DFS data gave these HR values: 2.1 (95% CI: 0.4–11.4; p=0.585), 4.2 (95% CI: 0.3–56.4; p=0.667), and 0.8 (95% CI: 0.1–4.7; p=0.772).

Summing up their findings concerning the polymorphisms investigated, Li observed, "We found that *TGFB1* rs1982073 had statistically significant associations with survival, while *TGFB1* rs1800469 and *TGFB1* rs1800471 did not."

Further Discussion

Regarding the TGF-β1 levels in patients, Li stated, "In this study, we found significantly higher expression of TGF-β1 in serum among HPV16-positive patients than among HPV16-negative patients. Furthermore, the patients with the variant genotypes of *TGFB1* rs1982073 were significantly correlated with increased serum TGF-β1 expression as compared to those with the corresponding common TT genotype; this similar correlation was also seen among HPV16 positive patients only.

"Although the functional relevance of this polymorphism has not yet been elucidated, our results might partially suggest a functional correlation between this polymorphism and expression of TGF-β1, providing preliminary evidence of biological plausibility for the observed association in this study," he further commented.

When asked about some of the limitations of their study, Li replied, "Some limitations [include the following]:

- As the majority (>90%) of the SCCOP cases in our study were non-Hispanic whites, our current results for generalizability to other ethnic populations may be limited.
- Because of relatively limited number of outcome events (death or recurrence) and duration of follow-up in this study, the significant associations could be found by chance.
- Some significant findings in the stratified analysis may have limited the interpretation due to the relatively small subgroup numbers in each subgroup.
- It is possible that misclassification of HPV status occurred in the HPV-negative group due to presence of other high-risk HPV types, leading to a bias of our results away from the null. However, this is unlikely to have occurred as we did not find a significant association in the HPV negative group."

When asked what direction some of the short-term research in this area may take, Li stated, "First, since the *TGFB1* rs1982073 polymorphism was significantly associated with survival in HPV16-positive SCCOP, that variant, together with other significant markers and details on radiation dosages, may help stratify HPV16-positive SCCOP patients for appropriate treatment strategies. Second, in order to validate our findings, larger, well-designed prospective studies may be required to more accurately evaluate the clinical validity and utility of this biomarker before implementation.

"Finally, future studies for exploring the molecular mechanisms underlying the observed associations are also needed," Li added concerning long-term research goals. OT

Richard Simoneaux is a contributing writer.