Leveraging Genomics in Head and Neck Cancer Research

For more than a decade, Gloria H. Su, PhD, Associate Professor of Molecular Biology in Otolaryngology – Head and Neck Surgery and Pathology at Columbia University Medical Center, and a member of the Herbert Irving Comprehensive Cancer Center at Columbia, has been studying the molecular genetics of head and neck squamous cell carcinoma, as well as pancreatic ductal adenocarcinoma. “These cancers are both results of accumulated genetic alterations,” says Dr. Su. “Both cancer types share some common oncogenes and tumor suppressor genes, but each has its unique targeted mutations. We hope to reveal new prognostic markers, discover tumor markers for early detection analysis, and develop chemo-preventive and therapeutic treatments that target tumor specific pathways.”

Using tissue-specific genetic-engineered techniques and their knowledge of the genetic profiles of human head and neck squamous cell carcinoma and pancreatic ductal adenocarcinoma, Dr. Su and her colleagues have successfully generated several mouse models that mirror the tumorigenesis of these cancers at both the genetic and histologic levels. “These models are now being interrogated to broaden our understanding of cancer development, progression, and metastasis, as well as the development of early detection and novel treatment options,” adds Dr. Su.

Implantable Neurostimulator Offers New Treatment Option for Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a highly prevalent disease in adults affecting an estimated 18 million Americans. Characterized by repetitive collapse of the upper airway during sleep, the recurring apneas cause hypoxemia and sleep fragmentation that lead to daytime sleepiness, increased risk for automobile and industrial accidents, depression, and overall reduction in quality of life. Some of the health problems associated with untreated OSA include cardiovascular disorders, hypertension, stroke, diabetes, and weight gain.

With sleep apnea, you don’t get restful or quality sleep,” says Maria V. Suurna, MD, an otolaryngologist in the Department of Otolaryngology – Head and Neck Surgery at NewYork-Presbyterian/Weill Cornell Medical Center. “Studies have shown there is a delay in reaction time for patients with sleep apnea. This is a concern for patients who drive automobiles or operate machinery, as there is a much higher risk for accidents. In addition, the cardiovascular implications of short- and long-term oxygen deprivation, such as increases in heart attacks, strokes, and high blood pressure, are well-documented.”

The mechanism of collapse involves a compromise in neuromuscular control of upper airway muscles and vulnerable airway anatomy. A person with OSA experiences reduced muscle tone during sleep,
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The PIK3CA Mutation in Head and Neck Cancer

According to the American Cancer Society, an estimated 59,340 people – 43,390 men and 15,950 women – will develop head and neck cancer in 2015. Progress over the past few decades in surgical techniques and radiation therapy have done little to improve the median survival of patients. Meaningful treatment and more successful outcomes are expected to be found in better understanding of the molecular and genetic features of head and neck cancer.

The focus of investigations of Dr. Su and her colleagues is the phosphoinositide-3-kinase catalytic (PIK3CA) gene – a known oncogene. “Previous studies had reported high frequencies of somatic mutations in the gene in several human solid tumors,” says Dr. Su. “In 2006, using the candidate gene approach, we found that the PIK3CA mutation is frequently activated in head and neck cancer. And in a subsequent study, we discovered that there is a higher percentage of this mutation in pharyngeal cancer and that the mutation is site specific. The importance of this gene/pathway has been validated with whole genome sequencing by multiple, independent labs, which demonstrated that there is a high frequency of PIK3CA mutations in head and neck cancer, but not just in that pathway.”

Dr. Su’s 2006 study has since been cited more than 100 times. Data from both studies provided evidence that oncogenic properties of PIK3CA contribute to the carcinogenesis of human head and neck cancers, especially in pharyngeal cancer. This opened the door to the possibility that a specific kinase inhibitor to PIK3CA may be an effective therapeutic reagent against head and neck squamous cell cancer or pharyngeal cancer in particular.

“Because PIK3CA and its pathway are possible targets for chemotherapy and radiation therapy, and frequent somatic mutation of PIK3CA has been identified in many human cancer types, including breast cancer and colorectal cancer, the ability to detect PIK3CA mutations with enhanced sensitivity has great potential impact on targeted therapies for many cancer types,” says Dr. Su.

Dr. Su believes this is a particularly promising avenue of research in light of a study by faculty in the Massachusetts General Hospital Cancer Center and Harvard Medical School published in the July 2014 issue of Cancer Cell that ties together the PI3K pathway and the CDK4/6 pathway in breast cancer. The study demonstrated that CDK4/6-PI3K inhibition could be an alternative therapeutic strategy for PIK3CA mutant breast cancer. “If you target both you can overcome resistance to the PI3K inhibitor,” says Dr. Su. “This is a logical approach for us to take in head and neck cancer. The difference is that we are using the spontaneous mouse model. It will be very compelling if we can show that their findings are applicable and visible in our mouse model.”

A Novel Mouse Model

Dr. Su’s lab has created a mouse model for head and neck cancer specifically in the oral cavity using PIK3CA as a driver. “Now that we know that this pathway plays a significant role in head and neck cancer, this mouse model can be used to look at effective, targeted therapy,” notes Dr. Su. “The model can also be used to investigate tumor heterogeneity and the mechanism for resistance and recurrence. In the meantime, whole genome sequencing and targeted therapy have escalated to the point where there are many drugs in the pipeline for therapies targeting the PI3K signaling pathway. This is a very exciting time as we begin to investigate targeted therapies for head and neck cancer using our mouse model. Our next challenge will be making the information clinically translatable and identifying patients who will benefit from the therapy.”

The head and neck cancer mouse model engineered by Dr. Su and her team expresses the oncogenic copy of the PIK3CA gene. It is conditionally activated by CK14-Cre in the oral cavity. It is also bred to p53-mutant background. Mutations in the p53 gene are among the most common abnormalities seen in human cancer. With the combination of Cre and carcinogen induction, these mice developed oral squamous cell carcinoma, mostly on their tongues. The non-transgenic control mice did not develop oral squamous cell carcinoma with the same carcinogen exposure.

“This model is unique because it represents a relevant genetic profile and histologic presentation to human head and neck squamous cell cancer,” says Dr. Su. “It could prove very valuable in testing targeted therapies, identifying biomarkers, and studying the tumor microenvironment because unlike xenograft models, it is a genetically engineered mouse model with an intact immune system. It can also be used to understand chemo-resistance and investigate metastasis because, importantly, the tumors in these mice metastasize.”

Dr. Su is also exploring the use of the exosomal biomarker to look for alterations in the PIK3CA pathway. “If we can find a profile that can be identified in this mouse versus other controlled mice that do not have the PIK3CA mutations in their tumors, we can use this approach as a way to identify PIK3CA as a specific exosomal profile,” explains Dr. Su. “This profile can then be verified in blood samples of patients with head and neck cancer and in patients who have mutations. From there, we can do a prospective study to see whether we can identify patients, blindly, verify if they have mutations in their tumors, and enroll them in chemotherapy. This information would be critically helpful for the development of new methods for early diagnosis, targeting therapy and monitoring response, and the eventual improvement in the survival rate.”

Reference Articles

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which predisposes soft tissues at multiple levels to obstruct the airway. The body’s natural defense mechanism temporarily awakens the individual, restoring muscle tone and temporarily dilating the airway, but the process repeats as one returns to sleep. The gold standard therapy for patients with OSA is CPAP—continuous positive airway pressure—which works by pneumatically splinting the airway open with positive pressure delivered via an airtight facemask attached to a bedside flow generator. “CPAP is very effective, but it must be used every night,” says Dr. Suurna. “The problem is that many patients are not compliant with this first-line therapy. Approximately 50 percent of patients diagnosed with OSA continue to use it long term. Patients don’t always like CPAP because it’s uncomfortable, bulky, and many patients are simply embarrassed to wear it.”

Upper airway surgery has been an alternative treatment option for many years. Several surgical procedures have been developed that modify soft tissues surrounding the upper airway either by tissue reduction or tissue stabilization and advancement. “Upper airway surgery is effective in properly selected patients, but without proper airway assessments, the results are limited,” says Dr. Suurna, who stresses the importance of first accurately evaluating the patient’s airway to determine the areas of airway collapse. “The best method we use today is through drug-induced sleep endoscopy—DISE. In the monitored setting we give patients some sedation to get them to the stage that would mimic natural sleep. Once they start showing signs of obstruction, such as snoring, we use a scope to see where the collapse occurs. In many patients the collapse happens at the base of the tongue. Surgery can work in patients who have favorable anatomy; however, the success rate is not as high as we’d like it to be.”

**Inspire® Therapy: A Promising New Option**

In 2014, the Food and Drug Administration approved Inspire® therapy for moderate to severe OSA patients who are intolerant to or have failed CPAP. The approach utilizes implantable neurostimulation technology—the first of its kind—designed to address tongue-based obstructions. Comprised of three implantable components, the Inspire® system employs a programmable neurostimulator, a pressure sensing lead that senses respiration, and a stimulation lead that delivers mild stimulation to the hypoglossal nerve, opening the airway during sleep.

“Inspire® therapy is a small, fully implantable system that continuously monitors the person’s breathing patterns during sleep and works with the body’s natural breathing process,” says Dr. Suurna, who notes that NewYork-Presbyterian/Weill Cornell is the first hospital in New York to perform an Inspire® therapy procedure. “The system is implanted under general anesthesia in an outpatient setting, allowing patients to return home the same day or early the next morning. Using a wireless handheld sleep remote, the patient simply turns the device on before bed and off upon waking. The device stimulates the key airway muscles, moving the tongue slightly forward during inspiration to keep the airway open during sleep.”

> “An important benefit of this treatment, as compared to other surgeries for sleep apnea, is that it preserves the natural airway and facial anatomy.” — Dr. Maria V. Suurna

Upper airway neurostimulation therapy has undergone multiple clinical studies since the late 1990s, and most recently was evaluated in a Phase 3, multicenter, international randomized controlled clinical trial. The STAR Trial enrolled patients who:

- have moderate to severe OSA
- were unable to achieve consistent benefits from CPAP therapy
- had a body mass index of ≤ 32
- passed a comprehensive airway anatomy examination

Results of the study published in *The New England Journal of Medicine* in January 2014 showed that Inspire® therapy can significantly reduce sleep apnea events and improve quality of life measures. These include a 68 percent median reduction in apnea-hypopnea index; a 70 percent median reduction in blood oxygen desaturation index; significant improvement in daytime functioning as measured by the Epworth Sleepiness Scale and Functional Outcomes of Sleep Questionnaire, and a measurable improvement in partner reported snoring. (Strollo PJ Jr, Soose RJ, Maurer JT, et al. Upper-airway stimulation for obstructive sleep apnea. *The New England Journal of Medicine*. 2014;370(2):139–49.)
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“Patients who may be candidates for the procedure must first undergo DISE to evaluate the nature of the airway obstruction,” says Dr. Suurna. “Once we have confirmed that the patient does not have circumferential velopharyngeal collapse, we then proceed with the implant. An important benefit of this treatment, as compared to other surgeries for sleep apnea, is that it preserves the natural airway and facial anatomy.”

According to Dr. Suurna, recovery from the surgical implantation of the device is significantly less painful and faster than recovering from palatoplasty, base of tongue reduction, or maxillomandibular advancement surgery. “Recovery from those procedures could take a minimum of two weeks,” she says. “With Inspire® therapy, the patient returns to their regular daily activities much faster. Then approximately four weeks after the procedure, the patient comes to the office to activate the device and to learn how to use it for the next 30 days. We then repeat the sleep study to determine how much the sleep apnea has improved and to optimize therapy settings. The patient returns once or twice a year for a device checkup.”

On May 15, 2015, Dr. Suurna performed the first upper airway stimulation implant surgery in New York and activated the implant four weeks later. “On July 20, a sleep study with final therapy titration was performed,” says Dr. Suurna. “The patient had a significant reduction of snoring and his overall AHI went from 50 events per hour to 0. This is a remarkable reduction in AHI. I’m very happy about the outcome for my patient and his family, and I’m excited about the future of this therapy for other patients suffering from obstructive sleep apnea.”

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