The Pathophysiology of Spasmodic Dysphonia: Dystonia and Motor Control Laboratory Dormancy via SOX9-and RARb-Driven Quiescence Programs

Kristina Simonyan, MD, PhD. Associate Professor of Neurology and Associate Professor of Otolaryngology

The pathophysiology of spasmodic dysphonia has eluded investigators. New techniques in neuroimaging, neuropathological, clinical, genetic and environmental correlates, led by Dr. Simonyan at Mount Sinai, have begun to identify the causes and potential therapies for spasmodic dysphonia. Using a variety of neuroimaging methods, including structural and functional MRI as well as positron emission tomography (PET) with radioactive ligands, Dr. Simonyan applies these research tools with clinical, behavioral and genetic testing in order to fully characterize the underlying causes and pathophysiology of SD and other focal dystonias. Recent advances in understanding dystonia included the first report of a group of patients with negative dystonia of the palate, which represents a novel and rare form of focal dystonia, impairing speech production (Sinclaire, Simonyan, Brin and Bliotzer in the June issue of the Laryngoscope). In this study, the group has defined the neural correlates of this form of dystonia in comparison with healthy subjects and patients with spasmodic dysphonia, identifying a unique pattern of brain abnormalities associated with negative dystonia of the palate.

Another paper by Kirke, Frucht and Simonyan in the June issue of the Journal of Neurology examined in depth the curious clinical phenomenon of alcohol responsiveness of dystonic symptoms in a large population of patients with SD and identified that more than 55% of SD patients have at least some positive benefits on their voice symptoms following alcohol consumptions.

This study opens potential new avenues of research for the development of novel therapeutic options for dystonia, in general, and spasmodic dysphonia, in particular.

In addition, as a longstanding research direction, Dr. Simonyan and her Dystonia and Motor Control Laboratory continue studies on normal motor control during speech production. Together they combine the available neuroimaging tools with computational neural modeling approaches in order to elucidate the organization of functional and structural brain networks underlying production of a spoken word in healthy individuals. Additionally, the laboratory uses graph theory to analyze functional MRI data recorded from speakers as they produce single syllables to whole sentences, revealing the complexity of the brain network machinery that controls speech and language. (Study by Stefan Fuertinger, Barry Horwitz, and Kristina Simonyan.)

How Tobacco use Impacts Prognosis in HPV-Associated Oropharyngeal Cancer Patients

While rates of laryngeal, oral, and hypopharyngeal squamous cell carcinoma have been decreasing as smoking has decreased in the US, the incidence of oropharyngeal squamous cell carcinoma has been rising. Common with this change, there has also been a change in the patient demographics. Worldwide, there has been a shift from a population of older patients (>60 years of age) with a strong history of tobacco and alcohol use to a younger population (<60 years of age) of patients with no or limited history of tobacco and alcohol use. These trends are a result of an epidemic of human papillomavirus (HPV)-associated oropharyngeal cancer. The significance of this epidemic is highlighted by the fact that HPV-associated oropharyngeal cancer in men will likely become more common than cervical cancer in women within the next 5-7 years.

Data suggests that the best survival rates are achieved in non-smoking HPV-positive patients (82.4%), followed by HPV positive smokers, HPV-negative non-smokers, and finally HPV negative smokers (57.1%). Investigators at Mount Sinai report new data demonstrating the Transoral Robotic Surgery (TORS) yields outstanding outcomes in the groups of patients that are at the high risk for recurrence and death, tobacco users. Researchers found smokers and nonsmokers had locoregional control rates of 96.3% and 94.4% and progression-free survival rates of 87.1% and 100% respectively.

85% and 94.1%, respectively. HPV-negative and HPV-positive patients had locoregional control rates of 87.1% and 100% and progression-free survival rates of 74.2% and 95.2%, respectively. Locoregional control rates for HPV-negative smokers, HPV negative nonsmokers, HPV-positive smokers, and HPV-positive non-smokers were 90.5%, 80.0%, 100%, and 100%, where-as progression-free survival rates were 72.2%, 80.0%, 92.5%, and 100%, respectively. Researchers continue TORS may be beneficial for the management of HPV-associated oropharyngeal cancer irrespective of smoking status.

A note from Eric Genden, MD MHA, FACS

Over the past decade, the worldwide prevalence of oropharyngeal cancer and thyroid cancer has increased at an alarming rate. It is estimated that our multidisciplinary team of basic scientists, clinicians, and translational scientists have established a series of unique clinical trials designed to achieve optimal cure rates with minimal treatment toxicity. In this edition of Research Focus we highlight just a few of the unique programs that have contributed to a better understanding of these diseases. I hope that you find this update informative as we strive toward curing this disease in a way that maintains the patient’s quality of life.
Molecular Epidemiology of Head and Neck Cancer
Director Institute for Translational Epidemiology

Paolo Boffeta, MD, MPH

Dr. Boffetta’s research group is leading the INHANCE (International Head and Neck Cancer Epidemiology) Consortium, a collaboration comprising the principal investigators of more than 40 large molecular epidemiology studies of head and neck cancer that are ongoing or have been recently completed. Overall, clinical and questionnaire data on over 26,000 cases & 54,000 controls, and biological samples from a majority of the study populations are available for collaborative projects. These studies have been conducted in various regions of the world.

Worldwide, an estimated more than 600,000 head and neck cancer cases and 325,000 deaths due to head and neck cancer occur each year. Head and neck cancers are a related group of cancers that involve the oral cavity, pharynx and larynx. While it is well established that tobacco and alcohol account for at least 75% of head and neck cancers on a global scale, important etiologic questions remain to be addressed: (i) the role of genes and their interactions with environmental factors, (ii) etiology in rare subgroups including young age at onset, and nonsmokers and nondrinkers, and (iii) a precise characterization of the role of human papillomavirus (HPV).

In head and neck squamous cell carcinoma (HNSCC) metastasis occurs each year. Head and neck cancers are a related group of cancers that involve the oral cavity, pharynx and larynx. While it is well established that tobacco and alcohol account for at least 75% of head and neck cancers on a global scale, important etiologic questions remain to be addressed: (i) the role of genes and their interactions with environmental factors, (ii) etiology in rare subgroups including young age at onset, and nonsmokers and nondrinkers, and (iii) a precise characterization of the role of human papillomavirus (HPV).

Researchers at Mount Sinai
Determine NR2F1 Controls Tumor Cell Dormancy via SOX9- and RARb-Driven Quiescence Programs

Julio A. Aguirre-Ghiso, PhD Professor,
Director of Head & Neck Cancer Basic Research and Hematology and Oncology

In head and neck squamous cell carcinoma (HNSCC) metastasis originate from disseminated tumor cells (DTCs). The team led by Dr. Aguirre-Ghiso recently published in Nature Communications a breakthrough study revealing how a transcription factor, NR2F1, and signals in the bone tissue induce dormancy of disseminated HNSCC cells. They took these findings and discovered that by combining two FDA-approved drugs, azacytidine and all-trans retinoic acid (a form of vitamin A) they restored the NR2F1-driven dormancy program stopping the expansion of HNSCC cells. In collaboration with colleagues at the University of Washington they used the HNSCC model and identified for the first time markers that pinpoint prostate cancer single DTCs that were dormant or actively proliferating. This work has led to the development of a clinical trial for metastatic prostate cancer and the approach can be applied to other cancers, such as head and neck and breast.

More information can be found at icahn.mssm.edu/headneckresearch