

Proceedings From the 2011 American Association of Oral and Maxillofacial Surgeons Research Summit

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In 2011 the American Association of Oral and Maxillofacial Surgeons and its Advisory Committee on Research Planning and Technology Assessment held the fourth research summit in Rosemont, IL. The biannual symposium, cosponsored by the American Association of Oral and Maxillofacial Surgeons, the Oral and Maxillofacial Surgery Foundation, and the National Institute of Dental and Craniofacial Research, aimed at fostering the collaboration of oral and maxillofacial surgeons and experts from different disciplines and basic science researchers. The ultimate goal is to improve the care of the oral and maxillofacial surgical patients through the advancement of translational and clinical research.

The major themes of head and neck cancer, obstructive sleep apnea (OSA), and craniofacial develop-

ment reflect areas in which oral and maxillofacial surgeons have opportunities to lead advances in diagnosis and directed care.

Head and Neck Cancer

Oral and maxillofacial surgeons are often involved in the diagnosis and management of patients with head and neck tumors. With the development of several established fellowship programs in maxillofacial oncology and reconstructive surgery, more oral and maxillofacial surgeons are becoming the primary surgical specialists involved in the management of head and neck cancer. Currently, there are 17 residency programs and 4 accredited fellowship training programs headed by fellowship-trained oncologic surgeons. The goals of this section of the research summit were to highlight some of the important advances in head and neck surgery as they relate to oral cavity cancer and to emphasize the increasingly important role of the oral and maxillofacial surgeon in the management of patients with head and neck cancer.

Role of Research by Oral and Maxillofacial Surgeons Treating Cancer, by Brent B. Ward, DDS, MD, University of Michigan: If a specialty is to have influence in a particular area of medical practice, its contribution to basic, translational, and clinical research cannot be overlooked. In the management of oral and maxillofacial pathology, several areas continue to be controversial, such as premalignant epithelial lesions for which no randomized controlled data are available to define standard treatment algorithms. Oral and maxillofacial surgeons' abilities to shape clinical care for patients with head and neck cancer will depend on their abilities individually and as a specialty to contribute to the medical literature. A survey of oral and maxillofacial surgeons involved in the management of patients with head and neck cancer found universal agreement that the most impor-

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tant contribution of investigators in this specialty to date was the consortium effort by Montes et al.¹ This study described the impact of maxillary squamous cell carcinoma (SCC) on occult neck metastasis in the clinically negative neck, and further showed that a group of surgeons from within the oral and maxillofacial surgical specialty could collaborate to complete a study that provided enough clinical data to make a meaningful and important contribution to the literature on head and neck cancer. Today, the ability of oral and maxillofacial surgeons to individualize treatment for patients is limited; however, with further understanding of the biologic profiles of head and neck cancer, they will be able to stratify patients according to risk and to deliver targeted therapies for patients. As oral and maxillofacial surgeons continue to evolve their clinical role in the management of patients with head and neck cancer, they will strive toward defining standards of care and discovering novel therapies.

Human Papillomavirus-Related Oropharyngeal Cancer, by Robert I. Haddad, MD, Dana Farber Cancer Institute, Boston, MA: Head and neck SCC (HNSCC) is an important public health problem worldwide. Each year, HNSCC constitutes 5% of new cancers diagnosed in the United States and 8% of those diagnosed worldwide.² The primary risk factors remain tobacco and alcohol abuse, but a growing number of cancers of the oropharynx are found in patients without these risks. Clinical, molecular, and epidemiologic studies of these patients have shown that the human papillomavirus (HPV) is associated with an increase in the incidence of oropharyngeal cancers in patients without a history of tobacco or alcohol use.³ Cancer of the oral cavity, however, still occurs, predominantly in patients with a history of substantial tobacco and alcohol use.

Patients with HPV-seropositive HNSCC exhibit the following characteristics: 1) youth (HPV-seropositive cancer is diagnosed in patients in their 40s or 50s, whereas smoking-related cancer is generally diagnosed in patients in their 60s or 70s), 2) predominantly oropharyngeal cancers, 3) basaloid histologic features, 4) predominance of the HPV-16 subtype, and 5) an excellent prognosis with high cure rates despite an often advanced stage at presentation.^{3,4} Risk factors for transmission of HPV include multiple vaginal and oral sex partners and young age at onset of sexual activity.^{5,6} Case-control studies have shown that the odds ratio for HPV-16 seropositivity in patients with oropharyngeal cancer is 14.4.⁷

HPV infection can be detected in tumor tissue through in situ hybridization, p16 immunohistochemistry (a biomarker for the function of the HPV-E7 oncoprotein), and polymerase chain reaction for amplifying integrated viral proteins.^{8,9} Recent studies have shown

that HPV-16 seropositivity in oropharyngeal cancer specimens is associated with a better prognosis than HPV-16 seronegativity.⁹⁻¹¹ In addition, the prognosis is best for nonsmokers with HPV-16-positive oropharyngeal cancer and worst for smokers with HPV-16-negative cancer. Total pack-years of smoking and p16 positivity are independent predictors of overall survival and disease-free survival.⁹

The finding that HPV-16 seropositivity improves prognosis has implications for the treatment of this subset of oropharyngeal cancers. The standard treatment for oropharyngeal cancer is radiation therapy with concurrent chemotherapy.¹² Because HPV-positive oropharyngeal cancers are associated with a better prognosis, current and planned clinical trials are assessing the possibility of decreasing the intensity of radiotherapy to improve the quality of life after treatment.

In summary, HPV-positive and HPV-negative oropharyngeal cancers are separate entities. HPV-positive cancers respond better to chemoradiation and are associated with a better prognosis and higher cure rates. Future trials will assess modifications in the treatment of patients with HPV-positive oropharyngeal cancer, with the goal of minimizing morbidity and maintaining high cure rates.

Sentinel Node Biopsy for Early Oral Cancer: Are the Findings Compelling? by Francisco J. Civantos, MD, University of Miami Hospital and Clinics, Miami, FL: Management of the clinically negative neck (N0) in patients with squamous cell carcinoma (SCC) of the oral cavity remains a challenge. Currently, there is no method to assess subclinical metastasis in early SCC of the oral cavity. Elective selective neck dissection is the standard for the staging and treatment of occult cervical metastases, but it is not without substantial potential morbidity.¹³⁻¹⁵

The sentinel lymph node biopsy (SLNB) has been used as a less invasive alternative for staging the N0 neck. This method has been validated in clinical trials assessing treatment for melanoma.^{16,17} Briefly, the tumor is injected preoperatively with a radiotracer (technetium-99m sulfur colloid) that is then detectable on nuclear imaging. The tracer enters the interstitial space, flows to lymphatic capillaries, and becomes trapped in contiguous lymph nodes. A handheld gamma probe is used to detect radioactivity in the neck and to locate nodes with substantial radioactivity (>10% uptake of the radiotracer), which are removed through a limited incision. The nodes are then assessed with advanced pathologic techniques that are not feasible when applied to larger specimens obtained by standard neck dissection.¹⁸

The American College of Surgeons Oncology Group Z0360 trial was a prospective multicenter study conducted at 25 institutions.¹⁹ The study in-

cluded 140 patients with T1 and T2 oral cancers with N0 necks. The primary tumor was injected with a radiotracer, and the primary tumor and sentinel nodes were excised (median, 3 nodes removed per patient). Subsequently, the incision was extended, and a completion neck dissection (levels I to IV) was performed. The primary outcome variable was the negative predictive value of SLNB results compared with results obtained by complete neck dissection (ie, do negative sentinel nodes predict negativity of the selective neck dissection specimen?). Of the 106 necks with negative SLNB results, 100 had no additional positive nodes (negative predictive value, 94%). The negative predictive value improved to 96% when finer sectioning and immunohistochemical analysis of specimens were performed. SLNB detected 90.2% of the 40 patients with positive nodes in the selective neck dissection specimen. The accuracy of SLNB results increased with the experience of the surgeon and was higher for tongue lesions than for lesions in the floor of the mouth. These findings corroborate those of other trials, including the multicenter European Sentinel Node Trial.¹⁸

In summary, SLNB can be applied successfully to cancer of the oral cavity. It allows for less invasive staging of the N0 neck than does selective neck dissection. Currently, SLNB seems to be most useful for low-risk patients with N0 necks who would otherwise undergo watchful waiting. Future goals include developing more selective radiotracers and improving the accuracy of SLNB by the adjunctive use of molecular techniques for the rapid analysis of sentinel nodes.

Personalized Targeted Therapies in Head and Neck Cancer, by Joseph A. Califano, MD, Johns Hopkins University School of Medicine, Baltimore, MD: Personalized cancer treatment is being actively sought with the goal of improving patient outcomes. The development of molecular techniques that can assess DNA, RNA, protein, and metabolites has increased the possibility of tailoring medical care to a specific tumor and its environment within a specific patient. Decreases in the cost of whole-genome sequencing have improved the possibility of gene-specific cancer therapy.²⁰

In contrast to standard cytotoxic chemotherapy, newer targeted therapies specifically attack signaling pathways required for the growth of cancers. Protein phosphorylation is involved in the proliferation and differentiation of cells and is carried out by protein kinases, such as tyrosine kinase.²¹ Tyrosine kinase inhibitors have been developed to block the constitutive activation found in many cancers.²² Epidermal growth factor receptor (EGFR), a tyrosine kinase receptor, has been shown to be overexpressed in most cases of HNSCC. Its presence has been associated with improved survival, probably because of the avail-

ability of drugs that target the pathway.^{23,24} Inhibition strategies include EGFR tyrosine kinase inhibitors and antibodies directed at EGFR. For example, cetuximab, a monoclonal antibody targeting EGFR, has been shown to improve 5-year survival rates when administered with radiotherapy for HNSCC.²⁵

The molecular biology of HNSCC is complex and results from the dysfunction of multiple interacting pathways. Mutations identified in HNSCC include p53, ras, and p16.²⁶ Finding mutations with the potential for targeting by novel drugs is the goal of cancer genomic screening. In general, it is easier to interfere with an overexpressed oncogene than to restore a tumor suppressor gene. One tumor suppressor gene, p53, leads to many human cancers because after loss of heterozygosity.²⁷ Currently, it is not possible to replace mutated tumor suppressor genes within the genome. Researchers are assessing the therapeutic potential of other genetic changes, including changes within promoters, changes in splice sites, and variations in DNA copy number. In addition, detection of genomic and promoter methylation holds promise for the diagnosis and treatment of HNSCC.^{28,29}

The ability to assess the entire genomic sequence within tumors offers the potential for the identification of novel targets that can result in targeted cancer treatment. Villarreal et al³⁰ reported success using personalized targeted therapy to treat a single patient with end-stage pancreatic cancer (disease free at >36 mo). In their study, they performed global genomic sequencing of the cancer and created a personalized xenograft to allow in vitro testing of potential drugs. An allelic mutation in a DNA repair gene was found that explained the in vitro and in vivo sensitivity of the patient's cancer to the DNA-damaging agent mitomycin C, a drug not typically used to treat advanced pancreatic cancer. Although this case is encouraging, use of genomic sequencing and in vitro screening for every cancer is currently cost prohibitive.

Advances in the understanding of the molecular biology of HNSCC provide the potential for targeted or personalized treatment. Continued progress depends on using high-throughput technology to identify novel therapeutic targets within the genome of these cancers.

Management of Obstructive Sleep Apnea

Research in Diagnosing and Treating Obstructive Sleep Apnea, by Peter D. Waite, MPH, DDS, MD, University of Alabama, Birmingham: Despite a references to sleep in Greek mythology, sleep remains a poorly understood topic. Obstructive sleep apnea (OSA) is a potentially life-threatening medical disorder with estimated prevalences of 24% and 9% in

adult male and female patients, respectively.³¹ A surgical intervention for OSA is often indicated when other conservative therapies such as continuous positive airway pressure (CPAP) are unsuccessful or intolerable to the patient.³² Maxillomandibular advancement (MMA), a procedure commonly carried out by the oral and maxillofacial surgeon, has proved to be a successful treatment option for OSA.³³ Despite an increase in popularity, there remains a critical gap in the understanding of the role of maxillomandibular advancement and its treatment efficacy in the management of OSA. Research in OSA is a relevant topic in oral and maxillofacial surgery and provides opportunities for interested oral and maxillofacial surgical investigators to develop novel and relevant contributions to the specialty and to improve overall health care.

Biomarkers for Obstructive Sleep Apnea, by Atul Malhotra, MD, Harvard Medical School, Cambridge, MA: OSA has definitive effects on cardiovascular and neurocognitive health.³⁴ Unfortunately, these detrimental effects are often clinically underappreciated early in the disease process, although serious morbidities are known to occur. Daytime somnolence in patients with OSA results in a 7-fold increase in motor vehicle crashes.³⁵ OSA also leads to increases in the risk of hypertension,³⁶⁻³⁹ myocardial infarction,⁴⁰ stroke,⁴¹ cardiac dysrhythmia,^{42,43} and sudden death.⁴⁴ As obesity rates in the United States increase, the incidence of OSA and its systemic sequelae will increase correspondingly.⁴⁵

Because of ethical and logistical barriers to withholding treatment from symptomatic and asymptomatic patients with OSA, definitive randomized clinical trials have been problematic.³⁴ Currently, the diagnosis of OSA is made through polysomnography, which can be difficult and expensive to perform. Recent studies have focused on the development of potential biomarkers for OSA. The ideal biomarker would have 1 of the following characteristics: 1) high sensitivity and specificity for detecting disease; 2) a dose-response correlation with the severity of disease; 3) an ability to detect a response to treatment and to allow the measurement of treatment efficacy; and 4) involvement in a known causal pathway that, when changed, provides a reliable surrogate outcome measurement.⁴⁶

Currently, no ideal biomarker exists. Candidates include high-sensitivity plasma C-reactive protein,⁴⁷ high-sensitivity interleukin-6, and soluble interleukin-6 receptor.⁴⁸ Markers of endothelial function, such as homocysteine, may also prove to be beneficial.^{49,50} A recent study has shown that decreases in C-reactive protein concentrations are associated with improved responses to multilevel surgery for OSA.⁵¹ Further assessment of these potential bio-

markers is needed to establish their relation to OSA and the response to treatment. A promising area of research includes the assessment of levels of candidate biomarkers in patients undergoing MMA.

Morbidity and Mortality Associated With Obstructive Sleep Apnea, by Naresh M. Punjabi, MD, PhD, Johns Hopkins University School of Medicine, Baltimore, MD: Partial or complete airway obstruction leading to apneas, hypopneas, and recurrent arousals during sleep characterizes sleep-disordered breathing (SDB) and OSA. Disruptions in ventilation during sleep lead to decreased blood oxygen content and its resultant effects on systemic health. OSA impairs cognitive function, work performance and decreases quality of life.⁵²

Only in the past 20 years has SDB become a research priority. With increasing rates of obesity, the National Institutes of Health sought to define the public health impact of SDB through research initiatives. The Sleep Heart Health Study⁵³ and the Wisconsin Sleep Cohort Studies⁵⁴ were established in response to these goals. These studies are ongoing prospective cohort studies investigating OSA and SDB as risk factors for cardiovascular disease.

Patients with OSA enrolled in the Sleep Heart Health Study have been found to be at increased risk of various systemic diseases. Patients with an increasing apnea-hypopnea index (AHI) have exhibited increased rates of hypertension.⁵⁵ Other analyses have shown a linear odds ratio between OSA and congestive heart failure in men younger than 70 years.⁵⁶ Of these men, those with an AHI of 30 or higher had a 68% higher risk of incident coronary heart disease than those with an AHI lower than 5.⁵⁶ In 2006, Mehra et al⁴⁸ found that, compared with persons without SDB, subjects with SDB had 4 times the odds of developing atrial fibrillation, 3 times the odds of nonsustained ventricular tachycardia, and nearly 2 times the odds of complex ventricular ectopy. In 2010, Redline et al⁵⁷ showed that men with moderate to severe OSA had an approximately 3-fold higher risk of ischemic stroke. In 2004, Punjabi⁵⁸ showed that subjects with moderate to severe OSA had higher rates of glucose intolerance, independent of other risk factors. Moreover, OSA was found to be associated with all-cause and cardiovascular disease-related mortality, independent of other variables; the association was highest for men 40 to 70 years old with an AHI higher than 30.⁵⁹

OSA and SDB have a substantial impact on cardiovascular health and mortality. Research in the form of randomized clinical trials is needed to optimize treatments that decrease the morbidity and mortality rates associated with increasing rates of OSA and SDB.

Phenotyping to Understand Obstructive Sleep Apnea, by David P. White, MD, Harvard Medical School, Cambridge, MA: OSA results from the repetitive collapse of various levels of the upper airway during sleep: behind the uvula, the soft palate, and the tongue. The etiologic pathogenesis of OSA varies considerably among patients, and proper treatment may require an individualized approach.⁶⁰

Four physiologic traits are believed to contribute to OSA: 1) airway anatomy; 2) upper airway response (pharyngeal dilator muscle control); 3) arousal response to respiratory stimuli; and 4) loop gain (ventilatory control instability).

Airway anatomy: It has been well documented that patients with OSA have small, collapsible airways. This defect may be due to a small bony compartment surrounding the airway (ie, mandibular or maxillary hypoplasia) or to an increase of soft tissue surrounding the airway (ie, obesity and increased parapharyngeal adipose tissue).⁶¹ Airway size has been extensively studied through imaging (computed tomography and magnetic resonance imaging) and acoustic reflection, but its physiologic status is best measured by the critical closing pressure, which represents the pressure in the airway above the point at which collapse occurs. Airway size depends on the intraluminal negative pressure created by diaphragmatic contraction and the extraluminal tissue pressure, which can be modified by contraction of pharyngeal dilators such as the genioglossus muscle.⁶⁰

Upper airway response: Collapsing forces on the airway are countered by the activation of pharyngeal dilators. This response is especially important in the anatomically deficient airway. The genioglossus is the best understood pharyngeal dilator; it contracts as the result of several inputs within a reflex pathway. The first input is negative pressure-induced activation of laryngeal mechanoreceptors after diaphragmatic contraction. This activation ultimately leads to stimulation of the genioglossus by the hypoglossal nerve. A phasic respiratory activation pattern also exists whereby the genioglossus is activated 100 ms before diaphragmatic activation, thereby preparing the airway for subsequent airflow. Although a person is awake, a tonic stimulus from stimulatory neurons (serotonergic and noradrenergic) also keeps the genioglossus active. This stimulus decreases during sleep, and this decrease leads to partial or complete collapse of susceptible airways.⁶² The individual variability in the recruitment of pharyngeal dilator muscles and the ability of these muscles to maintain a patent airway may lead to inconsistencies in the severity of OSA and the response to treatment.

Arousal response to respiratory stimuli: The threshold to arousal from sleep because of respira-

tory stimuli (negative pressure, increased CO₂ levels, and decreased O₂ levels) is highly variable between individuals.⁶³ Patients with compromised airways must remain asleep long enough to allow for the recruitment of pharyngeal dilator muscles, and those with low arousal thresholds may not remain asleep long enough to use the compensatory mechanisms outlined above. Repetitive arousals and obstructive events prevent proper pharyngeal dilation. A patient's threshold to arousal could be measured by decreasing the airway pressure to the point of limited airflow; such a measurement may serve as an additional means of individualizing treatment.

Loop gain (ventilatory control instability): The respiratory mechanism is tightly regulated to maintain CO₂ and O₂ levels within a narrow range by multiple feedback loops. Loop gain indicates the instability of these feedback loops and measures a patient's susceptibility to periodic breathing. Loop gain is quantified as the ratio between ventilatory response and ventilatory disturbance. The greater response to small disturbances, the greater the loop gain and overall instability. Furthermore, controller gain and plant gain are 2 variables that control loop gain. Controller gain indicates a patient's responsiveness to increases in CO₂ levels, whereas plant gain indicates the effectiveness of a level of ventilation in eliminating CO₂. A high plant gain is seen in cases of low functional residual capacity, decreased dead space, low cardiac output or metabolic rate, and high CO₂ levels.⁶⁴

Ventilator control instability (loop gain) is an important aspect in the development of OSA. The cyclic nature of the respiratory system with its complex feedback loops sets up predisposed patients to unstable patterns of respiration and upper airway muscle contraction, leading to airway collapse.

The anatomy of the upper airway, the response of the airway musculature, the arousal response to increasing CO₂ levels, and loop gain are 4 phenotypic traits that make relative contributions to OSA. A model has been developed to predict which of these traits plays the largest role in a given case of OSA. Modification of the appropriate contributors to a patient's OSA offers the potential for individualized therapy.

Cleft and Craniofacial Anomalies

Cleft and Craniofacial Research, by Timothy A. Turvey, DDS, University of North Carolina School of Dentistry, Chapel Hill: Facial clefts and craniofacial malformations provide an exciting field for investigation. Many unanswered questions remain regarding the extrinsic and intrinsic causes of clefts and other malformations. In unilateral cleft lip and palate,

why is the left side affected more than the right? Clefts affect all cellular layers but to different extents, leaving heterogeneous defects. Why are clefts larger at the nasal base than at the alveolus? Identifying the underlying etiology genetically and phenotypically would open the door for prevention and/or early diagnosis and subsequent management by gene therapy.

Unanswered clinical research questions on the treatment of clefts include determining the best time for repair, the type of closure, and defining a role for regenerative medicine. Strong mentorship and collaboration within oral and maxillofacial surgery are needed to answer these questions through evidence-based clinical and basic science research.

Research in Facial Development, by Ralph S. Marcucio, PhD, University of California, San Francisco: Craniofacial malformations are among the most common congenital defects. Although the genetic basis of many facial malformations has been elucidated, the diversity of phenotypes that results from a particular mutation is poorly understood. New insight into the role of the brain in facial morphogenesis has provided some clarity.

Holoprosencephaly is the most common developmental defect of the human forebrain, affecting 1 in 1,250 pregnancies and 1 in 16,000 live births.^{65,66} This condition can result from mutations in the sonic hedgehog (SHH) pathway or other signaling pathways; these mutations disrupt the midline facial patterning of the embryo. Curiously, mutations of the same gene within the SHH pathway can lead to a wide spectrum of facial phenotypes.

The SHH pathway plays a crucial role in patterned facial growth through its interaction with the forebrain, neural crest cells, and the frontonasal ectodermal zone.^{67,68} Sonic hedgehog signaling from the frontonasal ectodermal zone acts to control growth centers involved in the morphogenesis of the face, specifically the maxilla.^{67,68} Experiments have shown that the signaling can be inhibited by directed antibodies. A series of experiments producing various levels of SHH signaling in chick embryos has shown that decreases in signaling lead to a continuous narrowing of the frontonasal prominence, progressive hypotelorism, and medial maxillary rotation. Increases in SHH signaling lead to progressive midfacial widening and lateral divergence of the maxilla.⁶⁹ This work showed that alterations in SHH activity in the brain have predictable effects on midfacial size, shape, and growth, with a particular effect on facial width. The variation in facial width seems to range from the narrowed extreme (holoprosencephaly, cyclopia) from a complete absence of SHH signaling to the hypertelorism seen in the activating mutations of the

SHH seen in nevoid basal cell carcinoma (Gorlin) syndrome.

These findings suggest that variations in SHH signaling between the brain and the face contribute to normal midfacial variations in width, shape, and size. SHH signaling may be the mechanism by which genetic variation leads to phenotypic patterns in facial development and may have implications for diagnosis and treatment.

Growth Factor Regulation of Osteoblast Differentiation and Bone Quality, by Tamara Alliston, PhD, University of California, San Francisco: Bone derives its strength from a combination of size, shape, density, and material properties.⁷⁰ The material properties of bone (ie, bone quality) are derived from the bone matrix, specifically the extracellular matrix produced by osteoblasts and osteocytes.⁷¹ Bone mass and density have been well studied under normal conditions and in disease states (eg, osteoporosis and osteoarthritis), but little is known about the effect of bone's material properties and quality on bone disease processes.

The mechanical properties of the extracellular matrix are tissue specific and result in a range of moduli of elasticity.⁷² For example, the modulus of elasticity of the brain and the lung are low, whereas that of bone and teeth is much higher. The material properties of the bone matrix have been shown to be developmentally regulated and anatomically distinct, but the developmental mechanism remains unclear.⁷³

In a mouse model established for assessing the properties (elastic modulus) of the bone matrix independent of bone mass and architecture, transforming growth factor- β (TGF- β) signaling levels were found to correlate with bone matrix properties.⁷¹ Specifically, increases in TGF- β signaling led to bone deposition with decreased elastic modulus and hardness, whereas decreases in TGF- β signaling increased the hardness of the bone matrix. Subsequently, it was shown that TGF- β exerts its effects through a downstream transcription factor, Runx2, which affects osteoblast differentiation.⁷⁴ Deregulated TGF- β or Runx2 function was then found to be involved in osseous diseases associated with hearing loss, such as cleidocranial dysplasia.⁷⁵ This pathway seems to be essential for hearing because it is responsible for the formation of the distinctly hard bone matrix needed for cochlear function.

The focus of future studies is to further characterize the TGF- β signaling pathway and its effects on bone extracellular matrix quality. These studies may disclose the relation between the molecular and physical mechanisms that influence bone quality. Regulation of this molecular pathway could potentially serve as a therapeutic target for treating different systemic bone disorders.

Neural Crest Cells and Signaling Mechanism of Palatogenesis, by Yang Chai, DDS, PhD, University of Southern California: Cleft palate, a common congenital birth defect resulting from the failure of palatal fusion, has medical, psychological, social, and economic consequences. The palate develops from the ectomesenchyme and pharyngeal ectoderm derived from the cranial neural crest.⁷⁶ Overlying the palatal shelves are the oral, nasal, and medial edge epithelia. The medial edge epithelium is eventually removed by apoptosis and cell migration to allow for palatal fusion.⁷⁷

Mutations within the TGF- β signaling pathway have been found to be associated with cleft palate in mice and humans.^{78,79} TGF- β signaling is necessary for the proliferation of the palatal mesenchyme derived from the cranial neural crest; this mesenchyme provides palatal shelf growth and apoptosis of the medial edge epithelium required for palatal fusion.⁸⁰⁻⁸²

Because the murine palate and the human palate exhibit substantial genetic overlap and develop similarly, the mouse model has contributed greatly to the understanding of the molecular mechanism of palatal development. Conditionally knocking out the TGF- β 3 receptor in mice has led to a lack of cranial neural crest cell proliferation and complete clefting of the secondary palate.^{81,82} Recent studies have uncovered novel TGF- β signaling mechanisms through Smad proteins and p38 mitogen-activated protein (MAP) kinase pathways and can be replicated in the mouse model.^{83,84} Modulation of this pathway in mutated mice has been shown to allow for rescue of proliferative defects in palatal explants and the prevention of clefting.⁸⁵ Such modulation provides great promise for the manipulation of TGF- β signaling in humans for the prevention and treatment of cleft palate.

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