Department of Biological Sciences Seminar Blog
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Speaker: Dr. Heather Szabo-Rogers, University of Pittsburgh
Title: *"Insights into Craniofacial development from Beetlejuice and Unicorn"*

Beetlejuice, Beetlejuice, Beetlejuice… a Unicorn's Tail of Craniofacial Development

By: Collin Kessler

Dr. Heather Szabo-Rogers is an assistant professor from the Department of Oral Biology in the School of Dental Medicine at the University of Pittsburgh. Her research centers around the development and segmentation of the face and skull. The developmental cycle of cleft lip and cleft palate have been the primary focus of her recent work. These cleft abnormalities are present in approximately one in every seven hundred human births in the United States[2]. A cleft palate is a connection between the palate and the nasal cavity, most likely due to poor segmentation during development. Similarly, a cleft lip is an extension of a cleft palate where the nasal connection opening is present both in the lip and the roof of the mouth. Correctional surgery on infants has reduced the lifelong effects of the cleft palate but it is an invasive procedure and not always accessible throughout the world.

The genes associated with cleft lip and cleft palate are being investigated by Dr. Heather Szabo-Rogers in models that originate from Beetlejuice and Unicorn mouse lines. These mice share nothing in common with Tim Burton or J.K. Rowling, instead, their distinct cranial features have given them cranial protrusions like a unicorn or small cranial features like Harry the Hunter from the movie Beetlejuice – the man from death's waiting room who evidently has died from a shrunken head. These mice models serve as excellent systems to study the genetic causes of cleft lip and cleft palate

Dr. Szabo-Rogers has used the Beetlejuice and Unicorn mouse lines to provide distinct morphological models that can help elucidate the genetic origins of cleft palate and cleft lip. It is understood that the cleft affliction is produced early in the embryonic stage when nasal, maxillary, and mandible facial prominences develop. During this phase, growth factors stimulate migration, patterning, and differentiation of the face. Global changes to these growth factors can influence the shape and width of the face. This is observed in the *Beetlejuice (Bj)* mouse line where the mice have compressed faces when compared to the wildtype[1], serving as a model for cleft anomalies. In these mice, an opening in the mouth connects to the nasal cavity and exhibits the cleft palate. All the *Bj* mice mutants had a cleft palate while only 46% had a cleft palate associated with a cleft lip. Mice that have the *Bj* phenotype have a mutation in the *Prickle1 (Pk1)* gene[1]. The *Pk1* gene is part of the planar cell polarity (PCP) signaling pathway that leads to division and segmentation of tissues and organs. The goal of Dr. Szabo-Rogers is to use the *Bj* mutants to study *Pk1* mutations to determine *Pk1* function in the skull and cranial base.

To study *Pk1*'s role in cranial base development, the pituitary development of the *Bj* mutant was compared to the wildtype and the results were notable. The cavity for the pituitary gland in the *Bj* mutant was smaller and had different bone structuring than in the wild type mouse. This is likely due to the segmentation of the face that lead to a shorter face when compared to the wildtype. To determine the genetic relationship between the *Bj* mutation and clefts observed in the facial prominences, the *Unicorn* mouse line has been bred out to display the mid-facial cleft palate. To correlate genotype to phenotype the *Unicorn* mouse line was exome sequenced. Study of this mouse line has demonstrated that the septum is formed in two different structures that come together to make one functional unit. Genetic abnormalities in the segmentation genes *Sox9* and *Hedgehog* have demonstrated upregulation during palate formation. These genes may play a role in completing the separation between the palate and the septum. Although more work

is required to translate this data from mouse models to humans, it certainly is a promising start to better understanding the formation and subsequent prevention of cleft lip and cleft palate.

Works Cited

[1] Gibbs, B. C., Damerla, R. R., Vladar, E. K., Chatterjee, B., Wan, Y., Liu, X., … Lo, C. W. (2016). Prickle1 mutation causes planar cell polarity and directional cell migration defects associated with cardiac outflow tract anomalies and other structural birth defects. Biology Open, 5(3), 323–335. http://doi.org/10.1242/bio.015750

[2] Szabo-Rogers, H., Yakob, W., & Liu, K. J. (2016). Frontal Bone Insufficiency in Gsk3β Mutant Mice. PLoS ONE, 11(2), e0149604. http://doi.org/10.1371/journal.pone.0149604