Implications of Dental Research Goes Beyond Teeth

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Ryan Mott, student researcher at the Herman Ostrow School of Dentistry

Ryan Mott: Looking at Dentistry Beyond Teeth

Ryan Mott is a junior at USC majoring in Biological Sciences and minoring in Sculpture. Originally from Portland, Oregon, Mott hopes to pursue dental school after completing his undergraduate studies at USC. He has been involved as a student researcher at the USC Herman Ostrow School of Dentistry since Fall 2009, under the guidance of Dr. Tina Jaskoll and Dr. Michael Melnick. The Melnick-Jaskoll Lab, which focuses on the genetic bases of craniofacial development, was established in 1980. Today, one of the lab's main focuses is cytomegalovirus (CMV), a form of the herpes virus that has been linked to an astounding number of birth defects. Mott has dedicated the past two years of his research to studying this unique, yet surprisingly common, virus.

The reason Ryan finds his area of research so stimulating is because it is very holistic; it is not only related to the mouth or teeth, but it also pertains to the general health of an infected individual. This has furthered his interest in a dental career by demonstrating that dentistry goes beyond just treating dental problems and that dental professionals do play a large role in general medicine. While Dr. Jaskoll and Dr. Melnick's interest in CMV may have been rooted from CMV's affect on tooth morphology, the research conducted in their lab could potentially find a remedy for the virus, and thus help to eliminate a common cause for birth defects.

Cytomegalovirus (CMV): What is it?

CMV is usually harmless and most people who acquire CMV have very few symptoms and almost no long-term health consequences. In fact about 50-80% Americans contract CMV by the time they are 40 years old. The virus never leaves the body once it enters; however, it usually remains dormant as the immune system constantly monitors and maintains the virus's population in the body. CMV is spread contact with saliva, urine, or other body fluids of an infected person, but symptoms are usually harmless. The two instances where CMV causes serious damage are if the person's immune system is weakened either through immunodeficiency

viruses or organ transplants, or if it is contracted before birth; the latter of which is Mott's primary focus for his studies.[1]

Human CMV can pass through the placenta from the mother to the fetus at a critical point during pregnancy when it will involve the most long-term, debilitating effects. According to the Centers for Disease Control and Prevention, about 1 in 150 children are born with congenital CMV, and 1 of those 5 born with the infection will develop permanent problems, making it quite a common cause for birth defects.[1] Once a baby is infected with CMV before birth, it may develop vision, neurological, and developmental problems, all of which are unfortunately permanent.

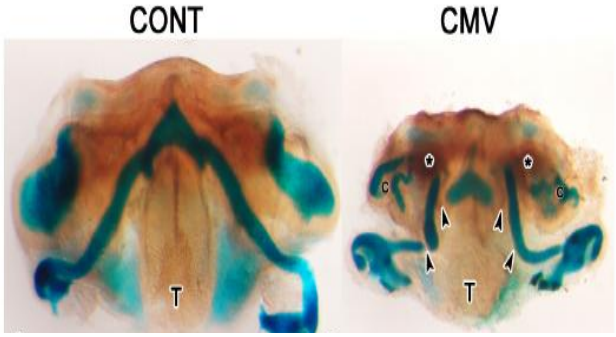

Figure 1 Shows the difference in morphology between the control (CONT) and the CMV induced blue stained cartilages and alizarin red-stained bone

A key feature of CMV is its large cells with intranuclear and cytoplasmic inclusion bodies ("cytomegalia"), which have been found in infected salivary glands. Figure 1 shows the difference between control and CMV-infected bone and cartilage. The virus sheds through the salivary glands, affecting tooth morphology—a key area of active research currently being conducted at the USC Dental School. While only 3-11% of healthy adults shed the virus through urine and saliva, about 50% of healthy children shed the virus through urine and saliva[6].

Using mice models, Dr. Jaskoll and Dr. Melnick have recently demonstrated that the submandibular salivary gland (the salivary gland located below the mouth floor), the mandible, and the teeth are all vulnerable to CMV infection during the critical stages of their organ development. Through embryonic mice explants, they have found that mCMV (mouse CMV) causes dysplasia, metaplasia, and anaplasia in salivary glands. Dysplasia refers to an expansion of immature cells, or abnormality in maturation, metaplasia refers to conversion of cells to the wrong types of cells, and anaplasia literally means "to form backward" and refers to a reversion of differentiation in cells.[4] Tooth morphogenesis is also delayed by mCMV-induced changes in the signaling pathways of mouse models[2]. The lab has also found that mCMV severely disrupts mandibular morphogenesis and skeletogenesis through changes in signaling pathways and unusual positioning of abnormal stromal cells, which make up the body's connective tissue[3].

Findings: A Possible Breakthrough?

Now that they know what areas are most targeted by the virus, Mott is working with the Lab in finding treatment or antiviral medications for this virus, which currently has no vaccine or cure. According to Mott, one of the biggest problems with using mice models is that "the mouse version of the virus does not pass through the placenta" requiring him to sacrifice the mothers in order to infect the embryos.

Mott's basic procedure involves sacrificing pregnant mice, dissecting out the embryo, and then taking out the salivary glands and ears. Once removed, these isolated parts are infected with CMV. Three sets are incubated: the control, the CMV infected tissue, and the CMV infected tissue with a specific drug or combination of antibodies that are used to try to block pathways. After incubation, the tissues are embedded in paraffin, and sectioned into ribbon-like pieces that

can be mounted on slides and stained for microscopy. Based on whether the cells are normal or mutated, it can be determined which antibodies work against CMV. Antibodies that have been tested include KCNQ1, Beta-catenin, Myosin 71, Amphiregulin, p120, Sonic hedgehog, and pERK. A potential breakthrough in the treatment of CMV depends on whether any of these antibodies are successful in combatting the virus.

Future Implications: How This May Revolutionize CMV Treatment

The Lab is in the process of publishing a paper on their research, but progress on mice models holds great potential for finding treatment options for infants who are infected with CMV. If an effective drug is found to work on mouse models, many doors are opened for clinical trials in the future. The next focus is shifting toward tumors and antibodies, and finding drugs that block pathways to tumor formation. It turns out that human CMV, while not an oncogenic (cancer-causing) virus, may actually infect tumor cells and increase their malignancy in a fashion not involving direct transformation[5].

Not only will CMV treatment help prevent congenital birth defects, but it may also help HIV/AIDS patients who are infected with CMV, as it becomes an opportunistic infection to those who have compromised immune systems. Being able to treat and cure patients with CMV infections is the ultimate goal, and the research conducted by Mott and the Melnick-Jaskoll Lab certainly brings us one step closer.

References:

1. Centers for Disease Control and Prevention. Overview. *Cytomegalovirus (CMV) and Congenital CMV infection*. 2010 [Online] http://www.cdc.gov/cmv/overview.html
2. Jaskoll, T, Abichaker, G, Jangaard, N, Bringas, P, Melnick, M. Cytomegalovirus inhibition of embryonic mouse tooth development: A model of the human amelogenesis imperfect phenocopy. *Archives of Oral Biology* 2008; **53**:405-415.
3. Jaskoll, T, Abichaker, G, Sedghizadeh, PP, Bringas, P, Melnick, M. Cytomegalovirus induces abnormal chondrogenesis and osteogenesis during embryonic mandibular development. *BMC Developmental Biology*, 2008;**8**:33.
4. Melnick, M, Mocarski ES, Abichaker, G, Huang, J, Jaskoll, T. Cytomegalovirus-induced embryopathology: mouse submandibular salivary gland epithelial-mesenchymal ontogeny as a model. *BMV Developmental Biology*, 2006;**6**:42.
5. Michaelis, M, Doerr, HW, Cinatl, J. The story of human cytomegalovirus and cancer increasing evidence and open questions. *Neoplasia*, 2009;11:1-9.
6. New York Department of Health. Cytomegalovirus. *Communicable Diseases*, 2006 [Online] http://www.health.state.ny.us/diseases/communicable/cytomegalovirus/fact_sheet.htm