Epigenetic regulation of cranial neural crest cells

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There is a fundamental gap in our understanding of how defects in chromatin remodeling proteins, methyltransferases and acetyltransferases are causative for human craniofacial phenotypes. This represents an important problem, because craniofacial defects occur frequently in the human population, 1 in every 1000 live births annually in the U.S. (CDC, 2011) and many are associated with epigenetic regulators of the genome. Our long-term goal is to better understand the function of chromatin remodelers during cranial neural crest (cNCC) development. We aim to determine the mechanism by which two families of epigenetic regulators, KAT2a lysine acetyltransferase and PRDM lysine methyltransferases that regulate each other and act to modify the same H3K9 residue on histone 3, function in zebrafish cNCC development. This excellent developmental model system, combined with genetic tools, live cell imaging of zebrafish cNCC behaviors and transcriptional studies will tackle the question of why mutations in *Kat2a* and *Prdms* lead to craniofacial abnormalities. We hypothesize that these chromatin modifying enzymes act as opposing transcriptional regulators and function cell autonomously to regulate cNCC proliferation and migration. We have determined that *Prdm1, Prdm3, Prdm16* and *Kat2a* have craniofacial defects in zebrafish. We have generated and obtained most of the zebrafish strains, and performed transcriptional profiling in both zebrafish, demonstrating feasibility. We have shown analysis of acetylation and methylation states in both tissue and biochemically. Cartilage staining of zebrafish embryos treated with drugs inhibiting methylation and acetylation show a craniofacial defect. In parallel, we are also analysing the epigenetic and transcriptional profile of mammalian cranial neural crest cells following such drug treatment. Our research has the potential to translate into a better understanding of the pathogenesis of craniofacial defects due to mutations in epigenetic regulators, including cleft lip and palate and various syndromes such as Kabuki and SBBYSS that affect the human population.