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Metastatic melanoma is notoriously resistant to chemotherapy. Interestingly, a recent study indicates that the enzymes that confer chemoresistance in metastatic melanoma cells are those that regulate pigment production in melanocytes. Melanocytes are a subpopulation of skin cells that produce pigment (melanin), for instance, during the tanning response. My work has focused on identifying the genes that regulate pigment production in melanocytes. We use zebrafish as an experimental model because they are easy to use and because regulatory genes are highly similar between zebrafish and humans. We have identified a gene family (Transcription Factor Activator Protein 2, TFAP2) that appears to be a master regulator of the genes encoding pigment synthesis enzymes. Thus, we found that when we remove TFAP2 from zebrafish embryos the development of melanocytes is strongly affected. Melanocytes in these animals are reduced in number and fail to produce equivalent amounts of pigment compared to a normal zebrafish embryo. Moreover expression of pigment synthesis enzymes is reduced within these embryos. Finally, we found that we were able to partially restore pigment production within these embryos by over-expressing another gene important in melanocyte development called MITF. In the project funded by the JM Nicolay foundation, I will continue to dissect the genetic pathway governing pigment synthesis in melanocytes. Further, I will test our prediction that manipulation of these pathways in metastatic melanoma cells will sensitize them to chemotherapy. This work is aimed at improving our understanding of pigment synthesis in melanocytes, and applying this understanding to design more effective therapeutic approaches for melanoma