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Role of Canonical Wnt Signaling in Melanoma

Nearly every melanoma-related death is due to the effects of metastasis, rather than to effects of the primary skin tumor. Melanoma is a highly metastatic cancer and metastasis can occur to distant sites in the body including lung or brain even with relatively small melanomas of the skin. Current treatment strategies for metastatic melanoma have little effect on overall survival, especially for patients with extensive metastasis at the time of diagnosis.

Metastasis is a very complex process and is very difficult to study in humans. Therefore, designing models of melanoma formation and progression are crucial to our understanding of this process. These models will help us to understand the differences not only between normal cells and melanoma cells, but also the differences between primary melanoma and metastatic melanoma cells. Understanding these differences will be important in helping to design new generations of cancer drugs that might help patients with metastatic melanoma.

Our lab generates new mouse models of melanoma in order to understand the basic processes of melanoma formation and progression. We study the genetic changes that make normal cells transform to cancer cells and also the genetic changes that lead to spread and growth of these cancer cells from the skin to other organs within the body. By creating mice with genetic changes that mimic those found in human melanomas, we are able to accurately model the disease in the sense that mice develop melanomas from the normal melanocytes found in their skin, just as a person would. These tumors can then be surgically removed and the metastatic process studied, also just as would occur in a melanoma patient.

This project focuses on genetic changes involving a signaling pathway within cancer cells that is particularly important to their ability to metastasize to the lymph nodes, liver, and lungs. We have been able to engineer mouse models where we can either ”turn up” or “turn off” metastasis simply by altering the status of one protein called beta-catenin, which is found within all melanomas. When beta-catenin has a mutation that makes it “over-active” melanomas metastasize with high efficiency to the lung or the liver. The site of organ metastasis depends on the other genetic mutations within the tumors. On the other hand, when the beta-catenin protein has a mutation that makes it “inactive”, melanomas fail to metastasize with any regularity. By examining beta-catenin signaling in cancer cells, it is our hope that not only will these models improve our understanding of melanoma metastasis, but also will lead to the identification of new drug targets that might bring us closer to finding a cure for melanoma.