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Using Melanocytes Derived From Pluripotent Stem Cells to Study Malignant Melanoma

Malignant melanoma is the most lethal form of skin cancer and its incidence continues to rise, particularly in young women. Yet our studies of this disease remain restricted by the limitations of currently used model systems. We propose to overcome these limitations by using melanocytes derived from human embryonic stem cells (hESCs). hESCs are cells that have the capacity to give rise to any cell type in the body. By harnessing the power of these cells, one can generate limitless quantities of any cell of interest, including melanocytes of human origin. We intend to use hESC-derived melanocytes to address two questions of interest to the melanoma field. First, we will determine whether the developmental stage of the cell of origin influences the malignancy of melanoma tumors. Secondly, we will investigate the roles of common melanoma-associated mutations using a combinatorial and sequential approach.

To establish a system for deriving melanocytes from hESCs we will mimic the stepwise progressive differentiation that occurs naturally during embryonic development. Since melanocytes arise from an intermediate population of cells known as the neural crest, we will first derive these cells from hESCs by optimizing an established method in our lab that spontaneously gives rise to low levels of neural crest. Subsequently the neural crest population can be guided towards the melanocyte lineage using signals known to be important for melanocyte development in the embryo. This approach will allow us to generate mature melanocytes with high efficiency and high purity suitable for subsequent melanoma studies.

The first question we will address using this system is whether the developmental stage at which a melanocyte acquires a mutation affects the malignancy of the resulting cancer. In hematopoietic cancers for example it has been shown that more stem-like cells will give rise to more aggressive cancers than when the same tumor-initiating event occurs in a more mature cell. Since our differentiation paradigm will mimic the processes that occur during embryonic development, we expect that we will be able to isolate both immature melanocyte progenitors as well as functional mature melanocytes. We will therefore introduce the same melanoma-associated mutations into both populations and ask whether there are differences in the resulting melanomas. This study may reveal the existence of melanoma subtypes that, due to their developmental origin, may exhibit different therapeutic responses.

It is known that melanoma does not arise from a single mutation, but requires the interaction of multiple oncogenic events. For our second question we therefore propose to use our hESC-derived melanocytes to investigate the sequential and combinatorial roles of different commonly observed mutations that enable tumor initiation and progression. We will introduce clinically relevant mutations alone or in combination and subsequently assay their effects on tumor behavior.

We believe that the project we have proposed will create a unique human model system for studying melanocyte development and melanoma progression and will contribute to a more comprehensive understanding of the sequence of events underlying melanoma oncogenesis and the developmental stage at which these events occur.