NORRIS COTTON CANCER CENTER | DARTMOUTH-HITCHCOCK MEDICAL CENTER

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NORRIS COTTON CANCER CENTER
THE ANDREA CLARK NELSON MEDICAL RESEARCH ENDOWMENT (THE ANDY FUND)
2010-2011 STATUS REPORT

The Andy Fund provides funding essential to Norris Cotton Cancer Center's research focused on cancer of the brain, especially glioblastoma multiforme. The Andy Fund enables investigators to pursue new ideas that may lead to more effective and patient-centered care. Promising scientists can develop preliminary research data that can then be used to pursue grant opportunities from external funding organizations such as the National Institutes of Health. By developing and sharing his/her research through publication and collaborative relationships, the investigator has an impact upon the scientific community at large and contributes to the process of discovery in cancer research.

The Andy Fund is managed by the Cancer Center Administration, and funding recommendations are made by the Cancer Research Committee (CRC) and submitted to the Director of Norris Cotton Cancer Center and the Dean of Dartmouth Medical School for approval. In its deliberations regarding allocation from The Andy Fund for 2010, the CRC recognized the specific purpose of The Andy Fund to support research in malignant brain tumors and chose to support the innovative research being undertaken by Dr. Huan Liu, working in the lab of Dr. Mark Israel.

Dr. Liu's work is focused on high-grade gliomas, which are the brain tumors that are the most difficult to treat. These tumors grow rapidly, outpacing the development of blood vessels within the tumor tissue. As a result, the vasculature is invariably inadequate to provide the nutriments and remove the wastes that such an active tissue produces. One of the critical growth requirements that are inadequately met under these circumstances is the need for oxygen to provide optimal energy production within the tumor cells. This lack of tissue oxygen, hypoxia, is a signature of virtually all invasive, rapidly growing brain tumors and their aberrant blood vessel formation. Direct measurement of oxygen levels and evaluation of various markers for hypoxia in human cancers have demonstrated that hypoxia is a characteristic feature of the solid tumor microenvironment. The finding that tumor hypoxia is an independent prognostic factor associated with advanced stages of malignancy and poor clinical outcome indicates the importance of hypoxia for tumor biology.

It has been demonstrated that tumor-derived stem-like cells, termed cancer stem cells, have a potent tumorigenic capacity and display increased resistance to radiation and chemotherapies. These findings highlight the importance of targeting the stem cells within a cancer for the development of more efficient cancer therapies. Therefore, elucidation of the mechanisms that regulate these tumor-derived stem cells may lead to improved cancer treatment. Alterations in many of the cellular pathways that are critical for regulating normal stem cells have been shown to promote the function of tumor-derived stem cells. However, recent evidence has suggested that the properties of tumor-derived stem cells can also be influenced by external signals from the environment.

It remains unclear how external factors present in the tumor microenvironment may regulate the characteristics of stem cells within a cancer, and this is the focus of Dr. Liu's investigations. Specifically, she has sought to determine whether hypoxia may promote the malignant phenotype of high-grade gliomas by regulating the function of tumor-derived stem cells. She utilized a tumor sphere culture system for glioma cells that has been shown to maintain the propagation of glioma-derived stem cells. She demonstrated that these tumor sphere cells displayed more malignant phenotypes in hypoxia, as indicated by the increased anchorage-independent growth in soft agar and enhanced self-renewal.

Dr. Liu also elucidated the importance of HIF-1α for the functions of these tumor sphere cells, and indicated that the activation of STAT3 in hypoxic conditions through HIF-1α may be an underlying mechanism through which hypoxia regulates the stem cell characteristics in tumors. These findings suggest that targeting this pathway, over which the central pathologic feature of glioblastoma cells is mediated, could be an efficacious therapeutic strategy.

Sincerely,

Mark A. Israel, M.D.
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