THE HARTWELL FOUNDATION

2016 Individual Biomedical Research Award

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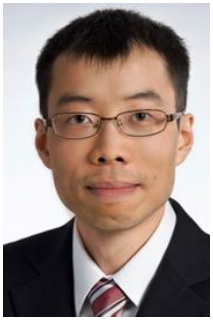

Inhibiting Anastasis in Cancer: Overcoming Reversal in the Cell Death Process to Prevent Recurrence

Despite dramatic scientific and technological advances, cancer remains a major and growing public health problem in the United States. Chemotherapy and radiotherapy kill cancer cells by inducing them to die through a cell death process called apoptosis (Greek for "falling to death"). While primary childhood cancers are often responsive to therapy and have low recurrence rates, most metastatic cancers, including childhood diffuse pontine glioma, lung and pancreatic cancers, typically recur. New treatments such as angiogenesis inhibitors that cut off the blood supply to tumors and targeted therapies that interfere with the cancer cell division have been developed to manage the disease, but are not a cure. With a high incidence of comorbidity associated with both the therapy and the recurrence of the cancer, the end results often mean a suboptimal quality of life for affected patients. Therefore, an urgent need exists for improved therapeutic strategies. In this regard, current cancer research is based on the general assumption that the initiation of cell death (*apoptosis*) is intrinsically irreversible. However, Hogan recently discovered that many human cancer cells can reverse the cell death process even at late stages and then survive. He named this recovery phenomenon *anastasis*, which is Greek for "rising to life". Simply removing the cell death-inducing cancer therapy can allow dying cancer cells to recover and then proliferate, suggesting that anastasis is a natural phenomenon. His discovery of anastasis is significant, because it reveals an unexpected mechanism that cancer cells can use to escape cancer therapy. Noticeably, most chemotherapy and radiotherapy are delivered episodically to let patients recover from the side effects between successive treatments. However, this approach may allow cancer cells to recover by undergoing anastasis during the intervals between cycles of anti-cancer treatments; cells may repopulate, leading to cancer recurrence. Unfortunately, some cells that reverse the dying process may acquire new mutations by harboring damaged DNA created during the cell death process induced by the therapy. The surviving cancer cells with DNA mutations may then contribute to cancer progression and increased resistance to drug therapy. Hogan intends to harness the discovery of anastasis to develop revolutionary new therapies to fight cancer by identifying drugs that suppress reversal of apoptosis. He will first seek to identify the regulators and mediators of anastasis, targeting the mechanism as a therapeutic strategy with potential to inform translation of novel anticancer drug therapies. If Hogan is successful, the result will be a paradigm-shifting therapeutic approach to cure cancer and prolong the life of affected children.