Functions of RB family proteins in human embryonic stem cells

Grant Award Details

Functions of RB family proteins in human embryonic stem cells

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Investigator:

Name:	Julien Sage
Institution:	Stanford University
Type:	PI

Disease Focus: Cancer

Human Stem Cell Use: Embryonic Stem Cell

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Grant Application Details

Application Title: Functions of RB family proteins in human embryonic stem cells

Public Abstract:

Nearly one out of every two Californians born today will develop cancer at some point in their lives, and it is likely that one in five persons will die of the disease. We propose to study the mechanisms of action of the RB gene, which is mutated in a broad range of human cancers, including pediatric cancers of the eye and the bone, and adult tumors such as lung, breast, prostate and liver cancers. RB normally acts as a tumor suppressor. When RB is mutated, cells lose the ability to sense when to cycle or not and they divide too much, thereby initiating cancer. Because RB is mutated in so many human cancers, therapies that could re-introduce RB function in cancer cells would benefit a great number of cancer patients.

A key question is to determine in which cell type loss of RB function is most detrimental. Knowing the answer to this question would help to diagnose cancer early and target specific cells within tumors, making treatment more effective. Recent evidence suggests that loss of RB may initiate cancer in stem cells . Because human embryonic stem cells (hESCs) give rise to any other stem cells, we will study the role of RB in hESCs. The results of these experiments will thus be applicable to a broad range of human cancers.

Specifically, we will use novel tools that will allow us to precisely alter RB levels in hESCs. We will then study the consequences of these manipulations for the proliferation of these cells; lower levels of RB may promote proliferation, while higher levels of RB may slow proliferation and push these embryonic stem cells to become more mature. We will then investigate the molecular mechanisms underlying these observations, beginning with the cellular pathway leading to retinal development because of RB's involvement in retinal cancer.

Because RB is usually deleted in cancer cells, there is no simple way to re-express RB function in these cells. However, two genes related to RB, p107 and p130, are rarely deleted in cancers and can compensate for loss of RB in mouse cells. Therefore, we will also study the role of p107 and p130 in hESCs, to determine if the functions of these two genes also overlap with RB function in these human cells and their progeny. If this is the case, knowing how to control the expression of p107 and p130 in hESCs may result in the development of a novel therapeutic strategy against human cancers associated with loss of RB.

A better knowledge of the cells from which cancer arises and of the molecular mechanisms by which cancer initiates will lead in the future to the development of novel means to diagnose cancer earlier, thereby increasing the chances of a successful therapy.

In addition, because of the central role of RB family members in multiple cellular functions, these experiments in hESCs may provide novel insight into the basic biology of these stem cells, which will eventually allow us to manipulate these cells more efficiently to treat a broad range of human diseases.

Statement of Benefit to California:

Despite significant decreases in the incidence and mortality rates of cancers in California over the past decade, nearly one out of every two Californians born today will still develop cancer at some point in their lives, and it is likely that one in five persons will die of the disease. Overall, in 2007, more than 50,000 people will die of cancer in California. These statistics underscore the need for the development of novel approaches to detect and treat human cancers.

Stem cells hold the promise of treatments and cures for human diseases that affect millions of people. In particular, recent models suggest that cancer may arise from mutant stem cells whose progeny form the bulk of the tumor. Thus, in the future, one anti-cancer strategy may be to replace mutant stem cells in patients with normal stem cells. Another approach may be to repair the defects in these mutant stem cells. However, these approaches will only be possible when the mechanisms controlling the proliferation of these stem cells and their capacity to produce their functional progeny are better understood under normal and pathological conditions.

We propose to study the mode of action of a key cancer gene, the RB gene, in human embryonic stem cells (hESCs). RB is inactivated in a broad range of human tumors, including adult lung, brain, breast, and prostate cancers, as well as pediatric eye and bone tumors. Thus, RB is a major target for the development of therapeutic strategies that may benefit a wide range of cancer patients. However, the mechanisms by which RB mutation triggers cancer are still poorly understood, hampering the development of such anti-cancer strategies.

We believe that by studying RB function in hESCs, we will gain novel insights into both the mechanisms of action of RB and the biology of these stem cells. Exploring the effects of altering RB levels in hESCs will increase our knowledge of RB's mode of action and will eventually provide new ways to treat human cancers. In addition, these experiments may identify novel means of manipulating hESCs to control the fate of these cells when transplanted into patients.

Because hESCs have the capacity to form any type of cell in the human body, these experiments will be relevant to the numerous cancer types associated with loss of RB function and may be ultimately translated into novel anti-cancer strategies. In addition, the results of these experiments may lead to novel avenues of research and may lay the groundwork for the development of therapies against diseases occurring in organs in which RB plays a central role, such as the eyes and the bones. Thus, the proposed research may benefit a broad range of patients, from young children to senior citizens, in California and elsewhere.
