University of Colorado
TECHNOLOGY TRANSFER OFFICE

Enhancement of Radiotherapy and Prevention of Tumor Repopulation, Metastasis, and Recurrence

UNIVERSITY OF COLORADO

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IP Status:
Patents pending; available for exclusive or non-exclusive licensing

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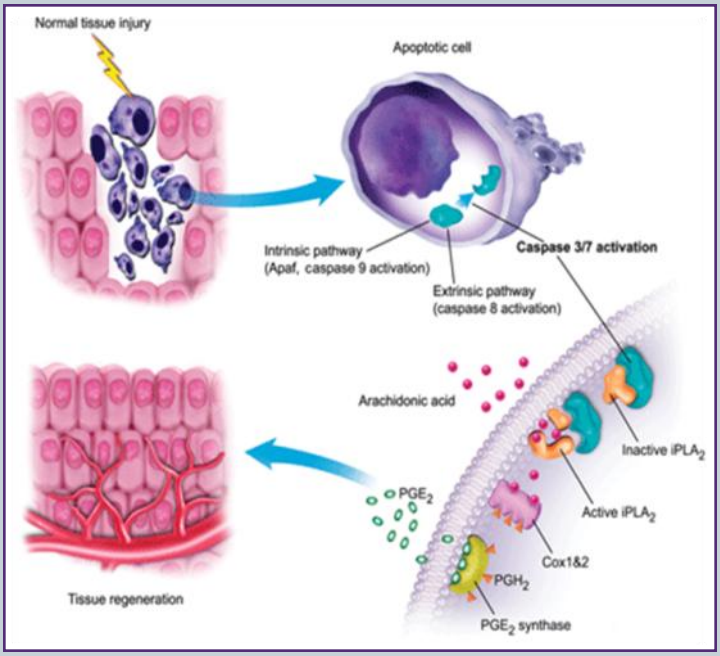
Background

Radiotherapy and chemotherapy are the current standards of care for most cancers. While these treatment methods eradicate the tumor, they also initiate a process called "accelerated repopulation." In this process, surviving tumor cells rapidly proliferate, repopulating the irradiated area at a significantly accelerated pace. Further complicating cancer treatment, radiation and chemotherapy regimens incorporate necessary intervals in treatment, allowing for the recovery, survival, and repopulation of normal cellular tissue. Unfortunately, these breaks in treatment, paired with "accelerated repopulation," allow for rapid growth of tumor cells. In fact, this issue of repopulation is a common cause of cancer treatment failure (see *Nature Reviews Cancer* 5, 516-525, July 2005) .

Technology

Dr. Chuan-Yuan Li, at the University of Colorado Cancer Center, has discovered a molecular signaling pathway integral in the process of "accelerated repopulation." With this scientific finding, Dr. Li has developed an approach to prevent tumor repopulation and metastasis, enhancing the effectiveness of cancer treatment.

In a recent publication, Dr. Li has shown that apoptotic cells release growth signals that stimulate the proliferation of progenitor cells (see reference below). He has identified Caspase-3 as a key factor in this signaling event. Dr. Li has discovered, using in vitro and in vivo models, that activated Caspase-3 is integral and required in signaling the rapid proliferation of surviving cancerous tumor cells. More specifically, Dr. Li has found that irradiation activates Caspase-3, and that by decreasing Caspase-3 expression, using shRNA, cellular growth of irradiated tumor cells can be significantly attenuated in vitro. Using an in vivo approach, Dr. Li irradiated cells genetically deficient in Caspase-3 and subsequently injected them into nude mice. Compared to controls, tumor cell-growth was decreased in the Caspase-3 deficient group by as much as 1000 fold. Further supporting the role of Caspase-3 in stimulating cellular growth, Dr. Li has shown that Prostaglandin E2, a promoter of cell proliferation and tissue regeneration, acts downstream of the caspases2 to facilitate stem cell activity and neovascularization.



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Applications

Dr. Li's work points to the promise of using Caspase-3 inhibitors to prevent tumor repopulation and metastasis following radiotherapy and chemotherapy. This work shows promise in the use of Caspase-3 inhibitors following irradiation to improve the prognosis of cancer patients. This synergistic approach may lead to reduced patient radiotoxicity and increased sensitivity to chemotherapy dosage.

Partnering Needs

- ⇒ Access to small molecule libraries for identification of caspase inhibitors optimal for radiosensitization and prevention of accelerated repopulation.
- ⇒ Evaluation of downstream pathway modulators: iPLA2 (Calcium independent Phospholipase A2) and Prostiglandin E2
- ⇒ Evaluation of the therapeutic concept in orthotopic solid tumor models

Data Update:

In vivo proof of concept has been conducting in the following models: Breast and colon cancer. Mouse xenograft: Breast cancer and colon cancer, using bioluminescence to monitor cell proliferation *in vivo*.

Key Documents

Apoptotic cells activate the "phoenix rising" pathway to promote wound healing and tissue regeneration. Science Signaling. 2010 Feb 23; 3(110):1-10. *PDF available upon request.*

Modulation of Caspases and Therapeutical Applications. U.S. patent application filed Jan. 5, 2011.

"Caspase Modulators and Methods of Use." Provisional patent application filed Jan. 6, 2010, available under CDA.