Inhibiting cancer stem cell survival in the hostile tumour environment

Wouldn’t it be great if a small non-toxic molecule could be used to treat cancer? By investigating the possibility of using a cancer cell’s own physiology as a weapon against it, Dr Shoukat Dedhar, at the University of British Columbia, is developing a new treatment that could help prevent tumour growth and metastasis.

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Inhibition of CAIX resulted in significant depletion of cancer stem cells within tumours

very difficult to eradicate every single one of them. If the cancer has metastasised (spread from the original tumour to another part of the body), surgery can rarely remove every cell, and treatments that typically kill cancer cells are generally toxic to normal cells as well. If even a few cancerous cells remain, they can cause a resurgence of the disease. Think of it like an ant’s nest – you can get rid of nearly all of them, but leaving just two or three could be enough for the nest to reappear down the line.

Current treatment methods involve the removal of cancer cells either through surgery or via radiation or toxic chemicals. However, cancer cells are tricky, and it is very difficult to eradicate every single one of them. If the cancer has metastasised (spread from the original tumour to another part of the body), surgery can rarely remove every cell, and treatments that typically kill cancer cells are generally toxic to normal cells as well. If even a few cancerous cells remain, they can cause a resurgence of the disease. Think of it like an ant’s nest – you can get rid of nearly all of them, but leaving just two or three could be enough for the nest to reappear down the line.

Dr Dedhar and his team are investigating a new type of treatment, which takes advantage of the unique physiology of cancer cells. It aims to inhibit their growth and ability to metastasise, without damaging healthy body cells.

The results so far have proved very encouraging.

A HOSTILE ENVIRONMENT

To understand how the new treatment works, we must first understand the inner workings of a tumour. Tumours are made up of millions of cells and, as each one grows, the blood supply required to nourish the rapidly dividing cancer cells with oxygen and nutrients becomes inadequate, causing regions of the tumour to become hypoxic (low in oxygen). Like normal body cells, cancer cells cannot survive without oxygen, so to overcome this, they stabilise a very important protein called HIF-1α (hypoxia inducible factor 1 alpha). This protein mediates the activation of numerous genes vital for the adaptation of cancer cells to the hypoxic environment.

Through HIF-1α, cancer cells in hypoxic regions of the tumour begin producing proteins that trigger the growth of hundreds of new capillaries. These new capillaries provide the tumour with additional oxygen and nutrients, whilst also removing waste products such as carbon dioxide. However, the capillaries are often leaky and deformed, so — although they allow the tumour to grow bigger and more quickly — the hypoxic micro-environments inside the tumour remain.

To compound the problem, hypoxic cancer cells alter the way they produce carbon dioxide. However, the capillaries are often leaky and deformed, so — although they allow the tumour to grow bigger and more quickly — the hypoxic micro-environments inside the tumour remain.

CAIX-Targeted Therapy is a Weapon used to Exterminate Hypoxic, Treatment-Resistant Cancer Cells

By targeting CAIX, we may be able to overcome resistance to chemotherapy and radiotherapy, tumour recurrence and metastasis

acidic waste products that build up inside and outside the cells. If cancer cells cannot adapt to the hostile, acidic micro-environment present in hypoxic parts of the tumour, they will soon die.

ADAPT OR DIE

As part of their adaptive response, cancer cells begin producing a cell membrane-bound protein called carbonic anhydrase IX (CAIX). CAIX converts carbon dioxide from outside the cell into bicarbonate and protons. The bicarbonate is then transported into the cell to reduce the intra-cellular acidity, providing a survival benefit for these cells. The protons remain outside and contribute to the acidification of the micro-environment. Creating this acidic environment causes cancer stem cells to divide more rapidly, enhancing their ability to invade healthy tissue and metastasise across the body.
The molecular basis and targeting of Dr Dedhar’s research focuses on the role of CAIX, a protein involved in cancer metastasis. His study, and others like it, have provided proof-of-principle data that CAIX inhibition could provide a therapeutic benefit in treating cancer.

Dr Dedhar believes that by targeting CAIX, we may be able to overcome resistance to chemotherapy and radiotherapy, tumour recurrence and metastasis. He and his team have a targeted small molecule inhibitor of CAIX and have shown that this inhibitor reduces tumour growth and metastasis in models of human cancer. Inhibition of CAIX in human breast cancer cells in the laboratory prevented breast cancer stem cells from dividing and replenishing the cell population in hypoxia. The team also tested the CAIX inhibitor in a mouse model of breast cancer, with CAIX inhibition resulting in a significant depletion of tumorous cancer stem cells. Combination treatment using the inhibitor with paclitaxel (a chemotherapy drug) was also found to enhance tumour growth delay and completely eradicate metastasis of cancer cells to the lungs, when compared to treatment with paclitaxel alone.

Dr Dedhar received his BSc (Hons) in Biochemistry from the University in 1984. He carried out a Postdoctoral Fellowship in the laboratory of Dr Erkki Ruosluh at the Burnham Institute, in La Jolla, California, USA.

Collaborators  • Dr Claudius Supuran  • Velichem Biotech, Inc.

Bio  Dr Dedhar received his BSc (Hons) in Biochemistry from the University in Aberdeen, Scotland, and his PhD from the University of British Columbia, Canada in 1984. He carried out a Postdoctoral Fellowship in the laboratory of Dr Erkki Ruosluh at the Burnham Institute, in La Jolla, California, USA.

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Research Objectives  Dr Dedhar’s research focuses on the role of IκK signalling in cancer progression, the molecular basis and targeting of osteosome clustering in cancer cells, and the therapeutic targeting of tumour hypoxia effectors, Carbonic Anhydrases IX and XII.

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