Scottish Government Health Directorates Chief Scientist Office

CHIEF SCIENTIST OFFICE

FOCUS ON RESEARCH

INVESTIGATION OF THE ROLE OF FOXO TRANSCRIPTION FACTORS IN TYROSINE KINASE INHIBITOR-INDUCED G1 ARREST AS POTENTIAL TARGETS IN CHRONIC MYELOID LEUKAEMIA STEM CELL ERADICATION

Researchers
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Aim
Chronic myeloid leukaemia (CML) is one of the few cancers in which it has been possible to identify a plausible drug target, the cancer gene BCR-ABL which drives the disease. Over the last 15 years the development of targeted drugs, such as imatinib, has immeasurably improved the lives of many patients. However, two key issues remain, (A) that cancer stem cells in bone marrow are insensitive to the effects of these new drugs and (B) that the new drugs block division of the cancer cells making them dormant and protecting them from being killed. As a result, while treatment induces remission in patients, it is not a cure. Evidence suggests that a family of proteins, the FOXO transcription factors, may be involved in making the cells dormant. These are proteins which can tell a cell to either stop dividing or to die. The aim of this study was therefore;
1.To investigate how the drugs block cell division in patient cells with a focus on the FOXO transcription factors.
2. To establish whether FOXO transcription factors are potential targets for curing CML.

Project Outline/Methodology
The project initially compared the activity of FOXO family members in CML and normal stem cells. We then went on to examine the effect of drug treatment (e.g. imatinib) on FOXO activity in CML cells. This included examining a dataset which measured changes in the cells following drug treatment. In addition, decreasing the levels of FOXO in CML cells was used to assess their potential as targets for eradicating the disease.

Key Results
In the bulk of CML cells, the presence of the cancer protein BCR-ABL leads to inhibition of the FOXO proteins by changing their localisation within the cell, making them unable to inhibit cell division or to induce cell death. Treatment with imatinib, and other members of the same drug family, inhibits the cancer protein BCR-ABL, in turn causing the FOXO proteins to become active. This in turn controls the function of a number of key proteins, rendering the CML cells dormant.
Paradoxically, we found that in the rare and most difficult to kill cancer stem cells from CML patients, FOXO proteins are active even before drug treatment and maintain these cells in a dormant state making them very difficult to kill. This finding suggests that the BCR-ABL cancer protein is somehow repressed in the cancer stem cells. Finally we show that by inhibiting all three forms of FOXO in CML cells we can sensitise these cells to imatinib treatment and reduce the number of dormant cells.

Conclusions
In this study we have demonstrated that dormancy in CML cells is controlled by FOXO proteins, suggesting that targeting the FOXO signalling pathway is key to eradicating dormant CML stem cells.

What does this study add to the field?
This is the first study of this kind to be carried out on primary human CML patient samples and confirms and adds to work which has previously been performed only in CML cells grown in the lab and mouse models of CML. It greatly enhances our understanding of the regulation of dormancy in CML stem cells and provides a platform from which to aim to manipulate stem cell dormancy for therapy.

Implications for Practice or Policy
Finding a way of targeting the drug resistance of CML stem cells should lead to a cure for the disease. This would allow patients to come off long term treatments with their associated side effects.

Where to next?
We wish to further examine the mechanisms involved in the repression of BCR-ABL signalling in CML stem cells with the aim of targeting these cells for eradication to cure the disease.

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