Inhibition of EZH2 might be new therapy of multiple myeloma

12 January 2017

In a study published in the scientific journal *Oncotarget*, researchers from Uppsala University show how the protein EZH2 affects the development of multiple myeloma, and that inhibition of EZH2 could be used as a new strategy to treat the disease. The tumour form multiple myeloma is today incurable and it has been challenging to improve therapy.

Multiple myeloma is a type of blood cancer where immune cells grow in an uncontrolled manner in the bone marrow. Current therapies can prolong the survival of multiple myeloma patients but the disease still remains incurable. In order to develop new treatment strategies increased knowledge is needed about the genetic alterations that cause multiple myeloma.

Researchers at Uppsala University have previously shown that abnormal chemical modifications of DNA-associated proteins (histones) that regulate gene expression patterns can be a unifying underlying mechanism for the development of multiple myeloma. The researchers studied the protein EZH2, which is involved in the chemical histone modification, and by treating tumour cells with substances that specifically inhibited EZH2 they could reduce survival of the tumour cells.

In a recent study the same research group, led by Professor Helena Jernberg Wiklund at the Department of Immunology, Genetics and Pathology, has identified a new mechanism that could explain the tumour promoting role of EZH2 in multiple myeloma. The researchers analysed the activity of a large number of genes in tumour cells that had been treated with an EZH2 inhibitor and they found four important oncogenes with a lower activity.

"The role of oncogenes in the development of cancer is to potentiate the survival of the cancer cell, which instead of undergoing cell death, as is usually the case when the cell is not functioning properly, continues to divide and proliferate. In our study we identified four oncogenes that showed lower activity in cells treated with the EZH2 inhibitor as compared to control treated cells. All four genes have previously been shown to be associated with the development of multiple myeloma. This confirms our previous findings that inhibition of EZH2 could be used as a means to treat multiple myeloma", says Helena Jernberg Wiklund.

But the researchers were puzzled by the fact that inhibition of EZH2 could decrease the activity of the oncogenes. The chemical histone modification that is performed by EZH2 leads to a lower activity of affected genes. Therefore, an inhibition of EZH2 should result in a reduced level of chemical modifications, which in turn should result in an increased gene activity.

"The answer is that there are other genetic factors involved, called microRNAs. In the cells treated with the EZH2 inhibitor we found two microRNA genes with increased activity and we believe that the oncogenes are regulated by these microRNAs. What happens then is that when EZH2 is inhibited there is a reduced histone modification at the microRNA genes. This leads to an increased synthesis of the microRNAs, which in turn decreases the activity of the oncogenes. This is a completely new mechanism for EZH2 action", says Helena Jernberg Wiklund.

More information: Mohammad Alzrigat et al. EZH2 inhibition in multiple myeloma downregulates myeloma associated oncogenes and upregulates microRNAs with potential tumor suppressor functions, *Oncotarget* (2016). DOI: 10.18632/oncotarget.14378

Provided by Uppsala University