Anti-myeloma agent opens for new treatment strategy

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The tumour form multiple myeloma is very challenging to treat and is still considered incurable. In a recently published study in the scientific journal *Oncotarget*, researchers at Uppsala University show how inhibition of the protein BMI-1 could be used as a new strategy to treat the disease.

Multiple myeloma is a type of blood cancer where immune cells grow in an uncontrolled manner in the bone marrow. New treatment strategies have prolonged the survival of multiple myeloma patients but there is still a high rate of relapses and development of drug resistance. To improve the treatment of multiple myeloma, increased knowledge is needed about the mechanisms behind the disease development.

Potential target for therapies

In the present study, the researchers have investigated the protein BMI-1 as a potential target for new multiple myeloma therapies. When they inhibited BMI-1 in cultivated myeloma cells they found that the cells' viability decreased and that a larger percentage of cells stopped dividing and died. Furthermore, inhibiting BMI-1 in combination with previously defined drug targets in multiple myeloma enhanced the anti-myeloma effects mediated by single target inhibition.

"We used the substance PTC-209, which we know inhibits BMI-1, and treated cultivated multiple myeloma cells. We used both cell lines that are continuously kept as cultivated cells, and cells that were purified from multiple myeloma patients, either newly diagnosed or at relapse. In all cases we found that a decreased cell survival, which indicates that PTC-209 has an anti-myeloma effect," says Mohammad Alzrigat, researcher at the Department of Immunology, Genetics and Pathology (IGP) and first author of the paper.

Epigenetic regulation

The research group at IGP has previously published results of their studies where it has become increasingly clear that epigenetic alterations are involved in the development of multiple myeloma. Epigenetic alterations are chemical modifications of the DNA that affect gene activity without changing the sequence of the DNA. The researchers now chose to focus on BMI-1 because it is part of a protein complex that is involved in epigenetic regulation and could therefore be a potential target for influencing the development of multiple myeloma.

"Our study showed that PTC-209 most likely functions as an anti-myeloma agent by inhibiting the production of BMI-1. We also saw that when PTC-209 was combined with other substances that inhibit epigenetic alterations, the myeloma cells' survival was reduced even further compared to when only PTC-209 was used. Our results have both increased our understanding of how epigenetic alterations affect cancer development and shown how inhibiting these mechanisms in combination could potentially be utilised for future treatment of multiple myeloma patients, especially at relapse," says Helena Jernberg Wiklund who led the study.

More information: Mohammad Alzrigat et al. The polycomb group protein BMI-1 inhibitor PTC-209 is a potent anti-myeloma agent alone or in combination with epigenetic inhibitors targeting EZH2 and the BET bromodomains, *Oncotarget* (2017). DOI: 10.18632/oncotarget.21909

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