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Single gene cluster loss may contribute to initiation/progression of multiple myeloma

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The loss of one copy of the miR15a/miR16-1 gene cluster promoted initiation and progression of multiple myeloma in mice.

The study is published online in *Blood Cancer Discovery*, the latest journal of the American Association for Cancer Research, by Marta Chesi, Ph.D., associate professor of medicine at the Mayo Clinic.

Multiple myeloma is a cancer of antibody-producing cells called plasma cells. It is preceded by a premalignant condition known as monoclonal gammopathy of undetermined significance (MGUS), in which abnormal plasma cells are present but do not expand. A hallmark of both MGUS and multiple myeloma is the detection of an M spike, which indicates the accumulation of an abnormal secreted antibody in the patient's blood.

"The risk of progression from MGUS to malignant multiple myeloma is approximately 1 percent each year, but the factors that contribute to progression are not well understood," said Chesi. "The purpose of our study was to model genetic risk factors that may contribute to initiation and progression of multiple myeloma. This understanding could eventually allow us to identify the mechanisms that increase the risk of progressing to multiple myeloma."

One copy of chromosome 13 is deleted in approximately half of patients with MGUS and multiple myeloma; however, the significance of this deletion on prognosis and disease progression remains controversial. Chesi and colleagues hypothesized that individual genes on chromosome

13 may promote disease initiation and/or progression.

The authors examined the impact of two genetic loci found on human chromosome 13—RB1 and MIR15A/MIR16-1—on disease initiation and progression. Both RB1 and MIR15A/MIR16-1 are considered tumor suppressor genes due to their roles in regulating cellular proliferation. The RB1 protein is known to be inactivated in many cancers, including multiple myeloma. A previous study demonstrated that deletion of MIR15A/MIR16-1 enhances proliferation of human B cells, and deletion of the gene in mice promotes development of another blood cancer, chronic lymphocytic leukemia.

In this study, the authors deleted a single copy of either Rb1 or miR15a/miR16-1 in wild-type mice and in a transgenic mouse model of multiple myeloma they previously developed. The authors found that deletion of one copy of Rb1 did not affect disease initiation or progression. In contrast, deleting one copy of miR15a/miR16-1 in wild-type mice significantly accelerated the development of an M-spike. Furthermore, the deletion of one copy of miR15a/miR16-1 in mice with multiple myeloma significantly enhanced the aggressiveness of the disease and led to increased expression of genes that promote cellular proliferation.

The authors also analyzed a genetic dataset of multiple myeloma patients and found that deletion of one copy of MIR15A/MIR16-1 in patient tumors was associated with increased expression of the same cellular proliferation genes that were upregulated in mice.

"Losing one copy of the MIR15A/MIR16-1 gene appears to promote tumor cell proliferation in both mice and patients," said Chesi. "For many years, we thought that deletion of chromosome 13 was just a byproduct of other genetic changes in the tumor and that it did not directly affect disease progression. Our study now demonstrates that

deletion of chromosome 13, and specifically deletion of MIR15A/MIR16-1, appears to alter the biology of the tumor.

"However, the fact that the entire chromosome 13, and not just MIR15A/MIR16-1, is lost in many cases of MGUS or multiple myeloma suggests that other genes on this chromosome are also likely to be important for pathogenesis," added Chesi. In particular, Chesi is interested in studying DIS3, another gene located on chromosome 13 that is frequently mutated in multiple myeloma. The authors were not able to assess its contribution in this study due to the lack of relevant mouse models.

A limitation of the study is that it was not possible to delete Rb1 or miR15a/miR16-1 only in myeloma cells due to technical restrictions of their mouse model. As a result, these genes were deleted in all cells, including immune cells, which could have led to indirect effects on disease progression, explained Chesi. However, Chesi added that results from additional control experiments indicate that the observed results are unlikely to be indirect, as transplanted tumors behaved similarly in both wild-type and miR15a/miR16-1-deleted mice.

More information: *Blood Cancer Discovery*, DOI: 10.1158/0008-5472.BCD-19-0068

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