Early Detection and Treatment of Myeloid Leukemia

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Overview

malignancies such as AML and MDS are usually aggressive and have a low overall survival rate. Recent studies demonstrated that specific mutations in hematopoietic stem cells occur years before the disease is diagnosed in individuals at high risk of developing myeloid malignancies. Therefore, there is a need to prevent disease development in those individuals. The group of Prof. Liran Shlush found that inhibition of a specific error-prone DNA repair mechanism (MMEJ) could reduce the likelihood to develop future myeloid malignancies in high-risk individuals.

Background and Unmet Need

Myeloid malignancies are a heterogeneous group of clonal diseases, which account for about a third of all newly diagnosed hematological malignancies. It is comprised of cancers in chronic and acute stages, including myelodysplastic syndromes (MDS), chronic myeloid leukemia, polycythemia vera, and acute myeloid leukemia (AML). Most myeloid malignancies have aggressive nature resulting in a low overall survival rate1.

Recent studies have shown that specific mutations in hematopoietic stem cells and progenitor cells can occur years before diagnosis and maintain almost normal function before transformation to overt disease2. High-risk subjects are likely to develop malignancy/pre-myeloid malignancy due to risk factors, including age, gender, medical history, genetics, or environmental exposure. While pre-myeloid malignancies mutations can be found among individuals destined to develop myeloid malignancies such as AML and MDS, they are also present in 20-30 % of healthy individuals. **Therefore, there is a need to prevent disease development in those individuals who are at risk for myeloid malignancies.**

The Solution

group of Prof. Liran Shlush found that specific deletions that are pre-myeloid malignancies events are caused by an error-prone DNA repair mechanism called the Microhomology Mediated End Joining (MMEJ) pathway. Therefore, they suggest downregulating the MMEJ pathway in high-risk subjects, to reduce their likelihood to develop future myeloid malignancies.

Technology Essence

The group of Prof. Liran Shlush demonstrated that recurrent MMEJ deletions occur predominantly in myeloid malignancies, specifically in the genes CALR, ASXL1, and SRSF2 (Figure 1). They further showed that the source for these deletions is DNA Double-strand breaks (DSB), which are erroneously repaired by the MMEJ pathway. They show that these deletions most probably result from intrinsic cellular conditions (rather than exposure to

external conditions) that cause DNA DSB.

Therefore, they suggest a method of treating or preventing pre-myeloid or myeloid malignancy in a subject in need, by administering to the subject an inhibitor of a component of the MMEJ pathway. This may include small molecules, RNA silencing, or any other possible method to reduce MMEJ activity.

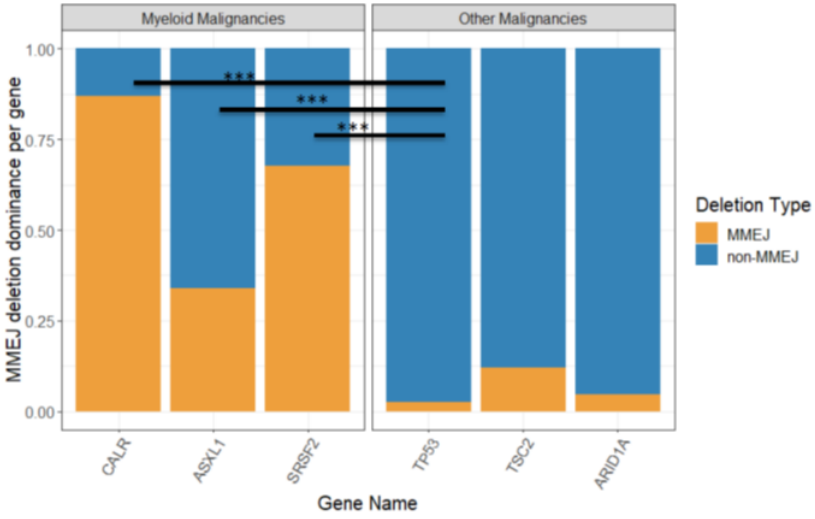

Figure 1 - recurrent MMEJ deletions occur predominantly in myeloid malignancies

Applications and Advantages

- Treating high-risk subjects before they develop the actual disease
- Creating a screening tool for the detection of preleukemic hematopoietic stem cells prior to mutation occurrence and disease progression

Development Status

The group identified and characterized the specific MMEJ mutations that cause pre-myeloid malignancy.

References:

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Shlush LI, Zandi S, Mitchell A, et al. Identification of pre-leukaemic haematopoietic stem cells in acute leukaemia. Nature. 2014;506(7488):328-333. doi:10.1038/nature13038 [2]

Patent Status

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