Master level degree project at the Bryceson Lab, Karolinska Institutet

Title

SAMD9 and SAMD9L: Understanding the pathophysiology of mutations that cause cancer and potential of these proteins to treat cancer

Background

Hematopoietic stem cells (HSC) reside in the bone marrow and sustain human hematopoiesis. To generate a variety of mature blood cells, HSCs undergo distinct processes including self-renewal, proliferation, and differentiation. Failure in any one of these processes can result in hematopoietic disorders and cancer. Among myeloid malignancies, myelodysplastic syndrome (MDS) is a hematological disorder where expansion of mutated HSCs cause impaired hematopoiesis and consequent decrease in peripheral blood cells. MDS frequently progresses to acute myeloid leukemia (AML) with poor outcome. Today, the only curative treatment for MDS is bone marrow transplantation.

Mutations in two homologous, evolutionary conserved genes called SAMD9 and SAMD9L are frequently reported in MDS patients, as we and others recently have demonstrated (Tesi, B. et. al; Blood; 2017). These genes represent novel tumor suppressors, assuming a critical role in the regulation of hematopoiesis. However, how SAMD9 and SAMD9L control cell cycle progression and why mutations in these genes give rise to myeloid malignancies remain unanswered questions.

Specific aims

The project aims to:

1) Identify molecular mechanisms through which SAMD9 and SAMD9L restrict cell proliferation
2) Understand how SAMD9 and SAMD9L mutations/deletions cause aberrant myeloid cell differentiation and proliferation
3) Explore mechanisms to fight cancer cells through activation of SAMD9 and SAMD9L proteins

Work plan

We plan to generate specific SAMD9 and SAMD9L gene variants to study their effects on protein regulation and function. Cells will be transfected with these constructs, followed by Western blot and flow cytometry analyses. A panel of SAMD9 and SAMD9L knock-out cells are already established in Bryceson lab, which will be used for co-immunoprecipitation and mass spectrometry analyses. A genome-wide CRISPR screening is planned and the results of screening will be validated using CRISPR-Cas9 system. Results will be validated in human stem cells or induced pluripotent stem cell lines.

Material and methods

- Molecular cloning and mutagenesis
- CRISPR-Cas9 genome-editing
- Cell culture, including stem cells
- Western blot analysis
- Co-immunoprecipitation
- Flow cytometry and cell cycle analysis
- Analysis and validation of mass spectrometry data

Contacts

Students who would like to join us and perform their master level degree project at Bryceson Lab (Karolinska Institutet), can contact Yenan.Bryceson@ki.se or saeed.eshtad@ki.se

As an alternative, students interested in doing a long individual project course are also welcome to consider us as hosting lab and apply to do so!