Werner syndrome helicase is a selective vulnerability of microsatellite instability-high tumour cells

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INTRODUCTION

Mismatches repair (MMR) deficiency causes microsatellite instability (MSI) in sporadic and hereditary cancer

Defective MMR (dMMR) & cancer:
- Loss of mismatch repair function
- MSIs in sporadic colorectal cancer
- MSI in Lynch Syndrome
- MSI in gastric cancer
- MSI in endometrial cancer
- MSI in colorectal cancer

RESULTS

Functional genomics indicates WRN as a dependency of MSI-H cells

MMS-H deletion
- Defective MMR (dMMR) & cancer:
- Loss of mismatch repair function
- MSIs in sporadic colorectal cancer
- MSI in Lynch Syndrome
- MSI in gastric cancer
- MSI in endometrial cancer
- MSI in colorectal cancer

Chromatin bridges and micronuclei in MSI-H cells after WRN loss

WRN is a selective vulnerability of MSI-H colorectal cancer (CRC) and endometrial cancer cell line

WRN helicase
- LOP mutations cause Werner Syndrome
- Homozygous loss of WRN function leads to loss of function
- LOF mutations cause Werner Syndrome

Cancer predisposition (Li-Fraumeni syndrome)
- Sporadic colorectal, endometrial and gastric cancer
- MSIs in sporadic colorectal cancer
- MSI in Lynch Syndrome
- MSI in gastric cancer
- MSI in endometrial cancer

WRN depletion experiments confirm the dependency of MSI-H but not MSS CRC cell lines on WRN

WRN depletion causes DNA damage in interphase MSI-H cells

Impact of WRN depletion on MSI-H cells
- Immunochemistry analysis after WRN depletion by siRNA
- Effect of WRN depletion by siRNA across cell lines based on functional genomic dataset from Project DRAGS (M.Donald et al., Cell 2017)

The interaction between MMR genes and WRN may not be hard-wired and absolute

Pharmacological inhibition of WRN helicase function might represent an opportunity to develop a novel targeted therapy for MSI-H cancers.

Open questions: mechanistic basis for MSI/dMMR- WRN link, relevance in patients?

SUMMARY

The dependency of MSI-H cells on WRN is not readily alleviated upon restoration of MMR gene products

Pharmacological inhibition of WRN helicase function might represent an opportunity to develop a novel targeted therapy for MSI-H cancers.

Open questions: mechanistic basis for MSI/dMMR- WRN link, relevance in patients?