ABSTRACT

Testicular germ cell tumors (TGCT) are the most common type of cancer in young men. Patients are successfully treated with a combination of cisplatin, bleomycin, and etoposide. However, 15-20% of patients are refractory to cisplatin treatment or undergo late relapse. We have previously shown that these refractory TGCT cells are highly sensitive to the DNA methyltransferase inhibitor, 5-aza. The 5-aza treatment demethylates the hypermethylated CpG islands in TGCT cells.

BACKGROUND

- DNA-demethylating agents target colorectal cancer cells by inducing viral mimicry by endogenous transcripts (Routois et al., 2015, cell 162, 986-997)
- Inhibiting DNA methylation causes an interferon response in cancer via dsRNA including endogenous retroviruses (Chiappinelli et al., 2015, cell 162, 974-986)
- Vitamin C increases viral mimicry induced by 5-aza-Z-deoxycytidine (Li et al., 2016, PNAS 113, 10226-10244)
- Most patients are successfully treated with a combination of cisplatin, bleomycin and etoposide. However, 15-20% of patients are refractory to cisplatin treatment or undergo late relapse
- Refractory TGCT are highly sensitive to DNA methylation inhibitor

AIM

To determine whether the mechanism of 5-aza hypersensitivity in TGCT cells is due to hyperactivation of immune surveillance pathways including the endogenous retroviral (ERV) dsRNA MDA5/MAVS/IRF7 pathway seen in colorectal and ovarian cancer.

- Experiment 1: Assess whether components of viral mimicry pathway and downstream interferon stimulated genes are induced in response to 5-Aza treatment
- Experiment 2: Knocking down core components of viral mimicry pathway and assess anticancer effects of 5-Aza in EC cells

RESULTS

- Interferon stimulated genes are induced with 5-aza treatment in EC cell lines
- Silencing shRNA validation
- Silencing antiviral sensors does not block the antitumor effects of 5-aza

CONCLUSION

- 5-Aza hypersensitivity in TGCT cells is not due to hyperactivation of immune surveillance pathways, but the pathway may be necessary for the survival of the TGCT cells

FUTURE DIRECTIONS

- Overexpressing the components of the viral mimicry pathway to determine any anticancer effect of 5-Aza in EC cells
- Knockdown of the components of the viral mimicry pathway in an in vivo model to assess any pro-survival effects of TGCT

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