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EACR 2023 Congress Abstracts

Contents

Proffered Papers

10-minute talks awarded for the highest scored abstracts, embedded in the scientific symposia sessions. These presentations are not accompanied by a poster.

Posters in the Spotlight

Tuesday 13 June, 17:30 - 18:30, Poster and Exhibition Hall
Wednesday 14 June, 17:15 - 18:15, Poster and Exhibition Hall

Dedicated sessions taking place in the spotlight area within the Poster and Exhibition Hall. Poster presenters with high scoring abstracts will give short presentations of up to 10 minutes. Their posters will also be available to view during the Poster Discussion Sessions.

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Merkel cell carcinoma cells

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Introduction

Merkel cell carcinoma (MCC) is a rare but aggressive skin cancer. About 80% of MCCs, are linked to oncogenic Merkel cell polyomavirus (MCPyV). Since the currently available MCC therapeutic options are remarkably limited, novel therapeutic approaches are required. The biological activity of all-trans retinoic acid (ATRA) is mediated by RAR/RXR receptors, which are ligand-dependent transcription factors that activate genes crucial for cell differentiation. Dysregulations of RAR/RXR receptors lead to carcinogenesis. Although a strong *in vitro/in vivo* antitumor activity of ATRA has been proved in different carcinoma types, the effect of this drug in MCC is still unknown.

Material and Methods

Herein, we investigated the antineoplastic effect of ATRA *in vitro* in MCPyV-positive (MCCP), i.e., PeTa and WaGa, and -negative (MCCN), i.e., MCC13 and MCC26, MCC cell lines and control, normal human lung fibroblasts MRC5. The antineoplastic effect of ATRA was evaluated by testing MCC cell proliferation, migration and colony formation abilities. Apoptosis/cell death were evaluated *via* Annexin-V and propidium iodide (P.I.) assays. Apoptosis was molecularly evaluated by RT^2 Profiler PCR mRNA array and by western blot (WB) analysis. Retinoic pathway was evaluated by RT^2 Profiler PCR mRNA array.

Results and Discussions

ATRA treatment led to a significant reduction in MCC cell proliferation, migration and clonogenicity, while increasing apoptosis/cell death in MCC cell lines compared to untreated cells. MCCP cells were slightly more ATRA-sensitive compared to MCCN cells. No significant effects have been found in the ATRA-treated control cell line. Gene expression array indicated a significant overexpression of several pro-apoptotic genes in MCC cells. High levels of pro-apoptotic proteins have been found following ATRA treatments in MCC cells, while being almost undetectable in untreated cells. Pro-apoptotic markers were almost undetectable in ATRA-treated MRC5. Numerous retinoic signaling genes, including BMP2, FOXA1 and MAFB, were differentially expressed in ATRA-treated MCC cells compared to untreated cells.

Conclusion

Overall, our *in vitro* data indicate that ATRA is effective in reducing MCC cell growth, while presenting strong pro-apoptotic effects and favoring cell death, by modulating the retinoic receptor pathway. These results, for the first time, point to ATRA as a potential novel effective antineoplastic drug for the MCC therapy.

EACR23-1190
Epigenetic targeting of MECOM dependency in ovarian cancers

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Introduction

Ovarian cancer is one of the most lethal gynecological cancers exhibiting poor survival rates and high incidences of cancer relapse. Patients develop resistance to standard chemotherapy while the use of targeted therapy is limited due to the non-availability of specific molecular targets. Hence, identifying targetable oncogenes that the tumor cells are addicted to, is required for better patient treatment and management. The Cancer Genome Atlas (TCGA) revealed 22% copy number amplification of MDS1 and EVI1 Complex Locus (MECOM) in tumor samples of ovarian cancer patients. The molecular function of MECOM is largely unknown. In this study, we unraveled MECOM as an oncogene regulating tumor cell proliferation that can be targeted directly or indirectly by epigenetic mechanism.

Material and Methods

Ovarian cancer OVSAHO and SKOV3 cells demonstrating copy-number amplification of MECOM were selected and overexpression was confirmed at RNA/protein levels. MECOM loss of function studies was conducted and tested for proliferation, cell cycle, and migration defects. Pan histone demethylase (HDM) inhibitor was used to understand the epigenetic regulation of MECOM.

Results and Discussions

MECOM silencing in OVSAHO/SKOV3 cells led to significant proliferation defects and G2/M arrest. MECOM deficiency also inhibited SKOV3 migratory potential by downregulating EMT genes. This is caused by a prominent reduction in ERK1/2 phosphorylation mediated by MECOM depletion. We investigated potential epigenetic ways to inhibit MECOM using available epigenetic inhibitors. We identified ZJIB-04, a pan-histone demethylase inhibitor, as an epigenetic regulator of MECOM expression. Interestingly, ZJIB-04 treatment led to proliferation defect, G2/M arrest, and diminished ERK1/2 signaling phenocopying MECOM depletion. We find that ERK1/2 signaling affected EGR1 levels which in turn reduced ZEB1 expression and reversed EMT. ERK1/2 signaling also mediated G2/M arrest by inducing GADD45A and GADD45B. ZJIB-04 most likely transcriptionally regulates MECOM expression via histone H3K9 methylation, which is under detailed investigation.

Conclusion

Collectively, our study demonstrates cancer cell dependency on MECOM for cellular proliferation and migration. Further, targeting MECOM directly or epigenetically by altering H3K9me3 might be a potential therapeutic strategy for MECOM-dependent ovarian malignancies.

EACR23-1193
The therapeutic potential of AZD-7648, a DNA-PK inhibitor, on acute myeloblastic leukemia

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