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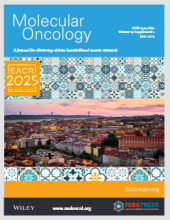

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Introduction

Inhibitors of ATR, a central kinase controlling DNA replication origin firing and cellular checkpoint activity, are currently in multiple clinical trials, yet mechanisms underpinning sensitivity and robust patient stratification biomarkers are lacking. In our new study we carefully characterized the mechanism underlying sensitivity to the important clinical target, the ATR kinase. Using an unbiased, multimodal approach in multiple cancer cell lines, AML patient samples and wider databases, we discovered an overlooked role for deregulated DNA replication origin firing in ATR inhibitor sensitivity.

Material and method

We used a non-invasive live microscope to monitor cell confluence in a panel of breast cancer cell lines to identify sensitive and resistant cell lines to ATR inhibition. We performed immunofluorescence microscopy to investigate rates of chromosome instability and replication stress. We then performed proteomics, phospho-proteomics and gene expression analysis to discover determinants of ATRi sensitivity. In parallel, we applied a newly developed machine learning coupled with long-read sequencing method to investigate DNA replication dynamics. Then, we used publicly available transcriptomic data from Cancer Cell Line Encyclopaedia and published Acute Myeloid Leukaemia patient data to investigate gene expression signature enrichment in larger datasets and including more cancer types.

Result and discussion

We discovered that all cell lines had increased levels of replication stress and chromosome instability upon ATRi, regardless of sensitivity. Interestingly, sensitive cell lines had higher expression and activity of DNA replication origin firing factors at basal. Moreover, in response to ATR inhibition, they massively increased origin firing, leading to the activation of the DNA damage response pathway and cell death. ATRi sensitivity was partly rescued upon co-treatment with XL-413, a CDC7 inhibitor that decreases origin firing. High expression of DNA replication initiation factors correlated with ATRi sensitivity across multiple cancer types, and in acute myeloid leukaemia patient samples.

Conclusion

Our study reveals that in sensitive cancer cell lines or patient samples, excessive origin firing is a detrimental response that leads to cell death. Moreover, this vulnerable state can be detected in sensitive samples by a higher level of origin firing-related factors, providing potential new and specific biomarkers for ATR inhibitor sensitivity that are compatible with clinical application.

EACR25-0543
LAMP1, LAMP2 and LAMP2A in colorectal cancer: potential prognostic biomarkers?

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Introduction

Lysosomal homeostasis and the dual function of autophagy, either suppressing or facilitating tumor growth, have been shown to play an active role in cancer biology. Dysregu-lated expression of lysosome-associated membrane proteins (LAMPs) has been demonstrated in various pathologies. Their augmented levels suggest potential involvement in tumor progression. The current study aimed to examine LAMP1, LAMP2 and specifically the LAMP2A isoform and to assess the clinical significance of serum protein and gene levels compared to their tissue expression in primary CRC and healthy individuals.

Material and method

Forty-one CRC patients (tissue as blood samples) and nontumorous colonic tissue and blood samples from healthy donors were examined by ELISA, qPCR, and immunohisto-chemistry.

Result and discussion

It was found that mRNA levels were significantly higher in CRC white blood cells than in healthy individuals. Additionally, the findings were supported by the apparent upregulated LAMP1, LAMP2 and LAMP2A levels in the CRC tissue immunostaining. The three examined proteins were observed within the tumor buds at the invasive front of the tumor in contrast to the feeble signal in tumor parenchyma and noncancerous tissue. However, while plasma protein levels of LAMP1 remained elevated in the patient group, LAMP2 exhibited a contrastingly higher pattern in the control group.

Conclusion

We present novel data for exploring the feasibility of LAMP1, LAMP2 and LAMP2A in liquid and tissue biopsy in CRC that could serve as future prognostic biomarkers for CRC stratification and treatment.

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EACR25-0554
Novel 1-benzhydryl piperazine scaffold-based HDAC inhibitor b7 induces synergistic antiproliferative effect with vemurafenib in colorectal cancer cells harboring BRAF mutation

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Introduction

Colorectal cancer (CRC) is heterogeneous malignancy characterized by variations in molecular profiles and clinical manifestations. Therefore, treatments for CRC are based on histopathological type and clinical stage of disease. However, in patients with metastatic CRC, available therapeutic options have shown limited effect. In recent years, histone deacetylases (HDAC)s have been identified as relevant contributors to pathogenesis and metastatic invasion of CRC. As HDAC6 is often over-expressed in CRC and correlates with poor disease prognosis it represents a good potential therapeutic target. The aim of this study was to evaluate antitumor activity of four novel HDAC inhibitors with 1-benzhydryl piperazine as a surface recognition group, that differ in hydrocarbon linker in HT-29 (with BRAFV600 mutation) and HCT-116 (BRAF wild type) human CRC lines.

Material and method

HT-29 and HCT-116 human CRC cells cultured in RPMI1640 cell culture medium (CM) were treated with b2, b3, b4, and b7 HDAC inhibitors and b3 and b7 in combination with BRAF inhibitor vemurafenib for 72h with at 37°C and 5% CO2 in humid atmosphere. Cyto-toxicity and IC50 values were estimated by MTT assay. Cell cycle analysis and PI/annexinV assay for apoptosis were performed by flow cytometry. Statistical differences between the control (CM) and treatment were estimated by one-way ANOVA and Student's t-test.

Result and discussion

b2 and b4 compounds with low potency for HDAC6 inhibition did not show any cytotoxic activity while b3 compound with higher potency for HDAC6 inhibition showed significant cytotoxic activity on HCT-116 and HT-29 cells with IC50 (μM) of 54.06 and 71.49, respectively. Furthermore, b7 panHDAC (HDAC1/3/6/8) inhibitor, which is potent in terms of HDAC6 inhibition, induced significant antiproliferative effect with IC50 (μM) of 22.04 and 58.99 for HCT- 116 and HT-29, respectively. Antiproliferative effects of b3 and b7 were more profound on HCT-116 cells and in both cell lines accompanied with increased apoptosis and alterations in cell cycle distribution. Furthermore, it was evaluated on HT-29 cell line weather b3 and b7 compounds could improve the effect of BRAF inhibitor vemurafenib. Cytotoxic effect of combination treatment of b3 and b7 with vemurafenib was evaluated by Chou-Talalay model. Our results showed synergistic effect of b7 and slight synergistic effect for b3 for concentrations lower than IC50 (12.5μM and 15μM, respectively).

Conclusion

Our findings of synergistic antitumor effect of HDAC and BRAF inhibition may provide rationale for investigations of their joint use in therapy of patients with CRC harboring BRAF mutation and evaluation of the potential of this therapy to increase response rate and overcome acquired resistance to treatment with BRAF inhibitors.

EACR25-0556
LOXL2 Inhibition: A New Strategy for Triple-Negative Breast Cancer

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Introduction

Lysyl oxidase-like 2 (LOXL2) is a member of the lysyl oxidase (LOX) enzyme family. These enzymes play a crucial role in the cross-linking of elastin and collagen, key components of the extracellular matrix. LOXL2 has been implicated in the regulation of tumor progression and angiogenesis, notably in triple-negative breast cancer [1]. This suggests that inhibitors of LOXL2 could offer potential therapeutic benefits in the treatment of this aggressive form of breast cancer [2]

Material and method

Computational docking studies were performed using previously reported inhibitors to explore their potential binding modes to LOXL2. In-house available compounds containing structures aligned with the computational chemistry insights, were screened for anti-LOXL2 activity using the Amplex Ultra Red assay [3]. A novel LOXL2 inhibitor was identified (AK75) that was then assessed in human triple-negative breast cancer cells (MDA-MB-231) and normal-like breast cells (MCF10A). The effects of AK75 on cell viability (MTT assay), migration (wound healing, single-cell tracking, and transwell assays), 2D and 3D invasion, cell morphology, DNA damage (γ-H2AX immunofluorescence), and matrix metalloproteinases (MMP) activity (zymography) were investigated.

Result and discussion

AK75 inhibits LOXL2 with an IC50 value in the very low micromolar range. This compound is not selectively cytotoxic for cancer cells and does not induce DNA damage. In MDA-MB-231 cells, AK75 reduces chemo-taxis, 2D and 3D invasion, MMP2 activity, and alters cell morphology.

Conclusion

This study explores the potential of AK75, a novel LOXL2 inhibitor, towards an eventual therapeutic strategy for triple-negative breast cancer treatment.

EACR25-0563
The DC6-KSP signaling Pathway is essentially required for Metabolic Adaptation and Leukemic Progression

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Introduction

Acute Myeloid Leukemia (AML) is a highly aggressive cancer originating from myeloid lineage stem cell precursors, affecting both adults and children. It is notorious for drug resistance and high relapse rates. While DC6 has been implicated in the progression of