Molecular Oncology

Volume 18, Supplement 1, June 2024

EACR 2024 Congress Abstracts

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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 11 June, 18:15 - 18:40, Poster and Exhibition Hall
Wednesday 12 June, 18:15 - 18:40, 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 5 minutes each. Their posters will also be available to view during the Poster Discussion Sessions.

Late-breaking Abstracts

Late-breaking abstracts are those for which full data were not available at the time of the regular abstract deadline.

Molecular Oncology 18 (Suppl. 1) (2024) 1–495

1482 compound library targeting cancer pathways and epigenetic modifiers.

Results and Discussions

High-resolution multi-omics analysis of longitudinal patient tumors and patient avatars identified patient-specific evolution of the primary tumors at recurrence following surgical resection and treatment pressure. While certain GBMs recurred without major molecular adaptation, others showed significant (epi)genetic and transcriptomic evolution towards new genetic clones and/or transcriptomic states. Majority of drug responses were similar in primary and recurrent tumors and were patient-specific. Interestingly, we observed selective susceptibilities to several epigenetic modifiers, especially Histone Deacetylase (HDAC) and Aurora Kinase (AURK) inhibitors in certain primary tumors, which were lost at recurrence.

Conclusion

Our study demonstrates the importance of combined omics and functional profiling to reveal clinical implications of longitudinal evolutionary trajectories in GBMs. Our findings imply that the impact of potentially effective drugs may differ between newly diagnosed and recurrent GBMs that might have implications in precision therapy strategies.

EACR2024-0301
Retrograde Trafficking in TNBC Stratification: Molecular Insights and Therapeutic Implications

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Introduction

Triple Negative Breast Cancer (TNBC), an aggressive and heterogenous subtype of breast cancer (BC), accounts for 15-20% of BC cases but a disproportionate 40% of deaths. Response rates to chemotherapy vary and the effectiveness of first line treatment forecasts overall survival, with poor outcome for non-responders. Predicting response remains elusive and alternate treatment options need identified for those not gaining benefit from current standard of care (SoC). Gene expression analysis of a retrospective TNBC patient cohort has identified several genes linked to retrograde trafficking (RT), associated with outcome. RT, which describes trafficking of cargo in a plasma membrane to Endoplasmic Reticulum direction is known to be dysregulated in cancer and disease. Therefore, we aim to investigate the therapeutic potential of targeting RT or associated intracellular processes, as our data indicates patients with high RT may not respond to SoC chemotherapy.

Material and Methods

In silico analysis of in-house and publicly available datasets was performed, correlating relapse-free survival and mRNA expression. Gene set enrichment analysis (GSEA) and drug sensitivity analysis was performed to identify molecular pathways related to RT. In vitro assays were used to assess cancer phenotypes following modulation of RT gene expression or treatment with RT associated drugs. Identified RT related pathways were investigated, including ferroptosis.

Results and Discussions

A gene signature based on the combined expression of RT genes Rab6A, COPZ1, VPS35, Rab2A, ANKFY1 and FAM21A was established and validated in large publicly available datasets. A high RT gene signature score was shown to significantly predict poor outcome in TNBC patients, while a low score predicted good outcome. Modulation of individual RT gene expression impacted cancer phenotypes including proliferation. GSEA using the RT gene signature, alongside drug sensitivity analysis pointed to a potential therapeutic vulnerability of inducing ferroptosis in patients with high RT highlighting an alternative treatment approach for poor outcome patients. Cell line models chosen to represent low to high RT showed response to ferroptosis inducers including RSL3 and erastin was strongly linked to RT score, however the exact molecular mechanism linking RT and ferroptosis remains unclear.

Conclusion

Our RT gene signature effectively predicts outcome of TNBC patients and highlights the potential of targeting RT-related pathways for more tailored treatment strategies.

EACR2024-0303
Extracellular vesicles derived from breast cancer cells rich in miR-23b-3p, miR-126-3p, and GAS5 inhibited the tumor growth of zebrafish xenograft model

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Introduction

Extracellular vesicles (EVs) are a group of nanoscale cell-derived membranous structures secreted by all cell types, which can commute biological cargoes for intercellular communication. They have notable roles in diverse physiological and pathological circumstances. Given their cargo, EVs as a mimic of "nature's delivery system" can be used to transport nucleic acids, proteins, and metabolites to target recipient cells. EVs offer a range of advantages over traditional synthetic carriers, thus paving the way for innovative drug delivery approaches.

Material and Methods

Here, we treated 4 different breast cancer cell lines (HCC 1937, MDA-MB-231, MCF-7, and MDA-MB-453) with sorafenib, which is a multikinase inhibitor. Then we collected their cognate EVs and characterized them using Western-Blot and Transmission electron microscopy (TEM) analysis. The levels of encapsulated miR-23b-3p, miR-126-3p, and GAS5 were quantified by Droplet Digital PCR (ddPCR). Moreover, to establish the role of the EVs as carriers of ncRNAs in vivo, we injected the MDA-MB-231 and MDA-MB-453 cells in zebrafish embryos and we treated the xenografts with two different types of EVs rich in miR-23b-3p, miR-126-3p and GAS5.

Results and Discussions
Results from ddPCR showed elevated levels of miR-23b-3p, miR-126-3p, and GAS5 following sorafenib treatment. Subsequently, utilizing EVs as carriers for these specific ncRNAs in breast cancer cell treatment led to a significant increase in the expression levels of all three ncRNAs, up to 7.5 times ($p<0.01$), along with a notable inhibition of cellular proliferation in vitro (up to 19%; $p<0.01$). In vivo experiments performed in zebrafish model demonstrated a remarkable reduction of xenograft tumor area (84%; $p<0.0001$, 24 hours post-treatment), suppression of angiogenesis, and decreased number of micrometastasis in the tails following the administration of EVs enriched with these ncRNAs.
Conclusion
Our findings indicate a new way to enrich EVs with specific tumor-suppressor ncRNAs by treating the cells with an anti-cancer drug; the role of EVs as vehicles of ncRNAs; the combined effect of miR-23b-3p, miR-126-3p and GAS5 in limiting the aggressive properties of breast cancer in vitro and in vivo. Our results may be useful to develop new potential molecular therapeutic strategies against breast cancer.

EACR2024-0304
Tumor-targeted extracellular vesicles carrying therapeutic siRNAs to suppress metastasis in medulloblastoma

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Introduction
The landscape of fatality in medulloblastoma (MB) mainly involves post-treatment recurrences in the form of metastasis. We recently identified *LOXL1-AS1* as a significant pro-metastatic long non-coding RNA gene in the sonic-hedgehog (SHH) subgroup of MB. To target *LOXL1-AS1*, small-interfering (si)RNAs allow both effective and specific gene silencing. However, the delivery of such therapeutic materials to brain tumors is extremely challenging. To this end, extracellular vesicles (EVs) are a powerful tool to protect siRNAs from in vivo degradation, promote penetration across physical barriers, and enhance tumor-specificity via surface display of targeting molecules. Our study aimed to develop a gene therapy model using siRNA-carrying and MB-specific EVs to target SHH-MB metastasis.
Material and Methods
An immortalized line of bone marrow-derived human mesenchymal stem cells (3A6) was used for EV production. A sequence coding for MB-specific cell-penetrating peptide (CPP) or an epitope tag (V5-tag, as control) was fused with the membrane glycoprotein Lamp2b and then transduced to 3A6 cells to establish stable line. EVs isolated from 3A6-conditioned serum-free medium were transfected with *LOXL1-AS1*-targeting (siLOXL1-AS1) or negative control (siNC) siRNAs, followed by RNase treatment and clean-up. EV characterization was performed using nanoparticle tracking, electron microscopy, qRT-PCR, and western blotting. After incubation with labeled EVs, MB cells were evaluated for fluorescent signals using flow cytometry and confocal microscopy or subjected to functional assays, including wound-healing, transwell migration, and sphere formation.
Results and Discussions
Generated EVs were smaller than 200 nm in diameter with intact membrane structure and enrichment of exosomal markers, Lamp2b protein, and V5-tag. MB cells treated with Lamp2b-CPP-EVs demonstrated a high level of EV uptake compared to those treated with Lamp2b-V5-EVs or other non-MB cell lines. SiRNA-transfected EVs had an encapsulation of ~400 siRNA copies per EV particle. MB cells treated with siLOXL1-AS1-EVs showed a reduced *LOXL1-AS1* expression and a significant inhibition in cell migratory and cancer stem-like features. An in vivo study using orthotopic xenograft mice intravenously injected with EVs is being evaluated for biodistribution, biosafety, and therapeutic effects.
Conclusion
Our study provides a promising EV-based siRNA delivery model for specific targeting and effective silencing of pro-metastatic genes in SHH-MB.

EACR2024-0305
Targeting Copz1 in in vitro mouse models of Thyroid Cancer

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Introduction
To sustain the neoplastic state cancer cells depend on normal genes, neither mutated nor aberrantly expressed, whose activity is not essential for normal cells. This dependency, known as non-oncogene addiction (NOA), could be exploited as a new strategy for cancer treatment, with the advantage of not affecting normal cells. We recently identified the coatomer protein complex ζ1 (Copz1) as an example of NOA for thyroid cancer (TC), for the aggressive forms of which no effective treatments are available. Copz1 vulnerability in TC is related to the down regulation of the Copz2 isoform. Our in vitro studies showed that Copz1 is essential for TC cells but not for normal ones. Copz1 silencing in TC cells induced endoplasmic reticulum stress that triggered inflammatory events and culminated in immunogenic cell death. To assess the effect and translational value of Copz1 depletion on cell-mediated immunity and inflammation, in vivo preclinical models are needed. Toward this aim, we have characterized the susceptibility to Copz1 inhibition of murine TC cell lines.
Material and Methods
We used the following murine TC cell lines: T4888M, T3531L, 3610R, 3868 and 3473. Real Time PCR (RT-PCR) was performed using TaqMan probes. Transient Copz1 silencing was performed by siRNAs transfection.