Molecular Oncology

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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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EACR23-1160
Resistance Mechanisms to c-MET inhibition in Hepatocellular Carcinoma

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Introduction
c-MET has emerged as a promising therapeutic target for hepatocellular carcinoma (HCC), and several clinical trials of c-MET inhibitors for HCC are currently ongoing globally. Capmatinib and tepotinib are two recently approved c-MET selective inhibitors by the FDA in 2020. However, the development of resistance in single-agent therapies is an inevitable challenge in clinical applications, which highlights the need to understand the mechanism of c-MET inhibitors resistance.
Material and Methods
A panel of HCC cell lines was treated with increasing concentrations of c-MET inhibitors. To systematically identify the kinase whose inhibition confers resistance to capmatinib in primary sensitive HCC cells, we conducted a CRISPR-Cas9 functional genetic screen. Multiple long-term colony formation assays and western blot were used to study the synergistic effects of the combination of c-MET inhibitors and other potential therapeutic inhibitors.
Results and Discussions
We identified that *PTEN* knockout leads to robust resistance to c-MET inhibitors in MHCC97H and HCCLM3 cells. Molecular mechanism studies showed that the level of AKT phosphorylation can serve as a biomarker for the response to c-MET inhibitors. Furthermore, suppression of c-MET in HCC leads to feedback activation of upstream receptor tyrosine kinases ERBB2 and ERBB3, which in turn upregulate the AKT signaling pathway and confer resistance to c-MET inhibitors. Therefore, drugs that inhibit both ERBB2 and ERBB3 can reverse unresponsiveness to c-MET inhibitors in c-MET-resistant HCC cells.
Conclusion
Our findings demonstrated the resistance mechanism for c-MET inhibitors in HCC. More importantly, we propose following solutions for HCC cell lines which are resistant to c-MET inihibitors: (i) combination of c-MET inhibitors and AKT inhibitor MK2206; (ii) combination of c-MET inhibitors and ERBB2/ERBB3 inhibitors Afatinib or Dacomitinib.

EACR23-1164
Nrf2 role in the BRAFi/MEKi acquired resistance in melanoma

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Introduction
Melanoma is one of the most aggressive cancers with the poorest prognosis. However, the use of specific inhibitors towards mutant BRAF (BRAFi) and MEK (MEKi) in BRAF-mutated patients has significantly improved progression-free and overall survival. Nevertheless, half of the patients still develop resistance within the first year of therapy. Therefore, understanding the mechanisms of BRAFi/MEKi acquired resistance has become a priority for researchers. In these last few years, scientists have focused on the role of NF-E2-related factor 2 (Nrf2), the master regulator of the cytoprotective and antioxidant response, in acquired chemoresistance. Indeed, its expression and activity are upregulated in various cancer types resistant to several chemotherapic drugs. The aim of this study was to evaluate the contribution of Nrf2 in the BRAFi/MEKi acquired resistance in melanoma, as well as the mechanisms of its activity regulation.
Material and Methods
Starting from BRAF-mutated murine melanoma cell line D4M, we generated three subclones resistant to BRAFi (dabrafenib, D), MEKi (trametinib, T), and BRAFi/MEKi (double resistance, D+T). Then, we evaluated cell viability (MTT test), anchorage-independent cell growth (Sphere Formation and Soft Agar Assays), apoptosis (Annexin V/IP), Cell invasion (Transwell Boyden chamber), angiogenesis (Tube-Formation assay), intracellular oxidative stress (2′-7′-dichlorodihydrofluorescein diacetate, DCF-DA, assay), glutathione (GSH) levels (Ellman's method), gene expression (western blot, real-time PCR), and gene expression inhibition with specific siRNA.
Results and Discussions
After nine months of continuous treatments with D, T or D+T, we obtained the three resistant subclones. Compared with the sensitive clone, the resistant sublines showed higher resistance to D, T, or D+T treatments and an enhanced ability to anchorage-independent cell growth with increased migration and angiogenic capacity. These results allowed us to consider these cell lines good models of resistant melanoma cells toward targeted therapies. These cells showed increased oxidative stress and GSH levels. Nrf2 was upregulated at post-translational levels, with the involvement of deubiquitinase 3 (DUB3). Interestingly, Nrf2 or DUB3 inhibition sensitised cells to targeted therapies.
Conclusion
Nrf2 can contribute to the mechanism of targeted resistance in melanoma. A complete understanding of its role can contribute to developing increasingly effective therapies in advanced melanoma.

EACR23-1171
Cross-talk between TNBC cells and adipose mesenchymal stem cells contributes to maintaining a hostile acidic microenvironment and increases PDL-1 expression

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