Selinexor (XPO1 inhibitor) in Combination with Tepotinib (MET inhibitor) Potentially Inhibits SHOC2 and KRAS G12C in KRAS G12C Mutant Non-Small Cell Lung Cancer


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Introduction
KRAS-mutant cells depend on SHOC2 and MET for anchorage-independent growth, suggesting the potential efficacy of MET inhibition against KRAS mutant tumors (Boned del Rio et al., PNAS 2019; Fujita-Sato et al., Cancer Res 2015).

SHOC2 deletion sensitizes KRAS and EGFR-mutant NSCLC cells to MEK inhibitors, preventing MAPK pathway reactivation (Ames et al., Nature Communications 2019; Sudhian et al., Cell Reports 2019).

Several research groups have demonstrated that SHOC2 binds PP1C and MRAS through its concave surface within the leucine-rich repeat region. High-resolution crystal structures of the SHOC2:MRAS:PP1C complex have been reported, setting the basis for the discovery of new classes of inhibitors. This trimeric complex forms exclusively when MRAS is in an active state, leading to PP1C-mediated RAF dephosphorylation (Liu et al., Nature 2022; Bonsor et al., Nature Structural & Molecular Biology 2022; Kwon et al., Nature 2022; Hausman et al., Nature 2022).

Additionally, XPO1 has emerged as a potential therapeutic target in KRAS-mutant NSCLCs (Kim et al., Nature 2016). We used an in-silico approach to investigate whether tepotinib (a MET inhibitor) and selinexor (an XPO1 inhibitor) can bind within the KRAS G12C His-95 groove, similar to sotorasib (a KRAS G12C inhibitor). We also explored their binding affinities for the trimeric SHOC2:MRAS:PP1C holoenzyme, with celastrol (a SHOC2 inhibitor) serving as a positive control.

Results

Based on the graphical representation of the binding affinities of both the target proteins, a similar score was observed for the ligand selinexor targeting both the proteins which were higher in comparison with their standard inhibitors. Tepotinib showed extremely high binding affinity with SHOC2 complex. Tepotinib showed a higher binding affinity with KRAS G12C in comparison to sotorasib.

Structure Complementarity of GDP bound KRAS G12C with the ligands, tepotinib and selinexor, in comparison to standard inhibitor, sotorasib, docked in the HB895 groove of switch II pocket. Tepotinib shares two hydrogen bonds binding to the HB895 groove of the binding pocket. Selinexor shares similar binding complementarity with sotorasib, sharing six hydrogen bonds, making it an excellent inhibitor to pave the way in in vitro studies.

Conclusions

Although KRAS G12C covalent inhibitors, such as sotorasib, can be combined with other therapeutic targets, early adoptive resistance can occur by a regulation of MRAS, as recently reported. Bioinformatic analysis indicates that various drugs, through non-covalent interactions, have binding affinity for the KRAS G12C pocket, as well as for the trimeric MRAS:SHOC2:PP1C complex which can lead to reactivation of MAPK pathway. The assessment of MET inhibitor, tepotinib, is of great relevance since MET is expressed in KRAS-mutant lung adenocarcinoma and selinexor is also of interest, since KRAS-mutant cell lines overexpress XPO1. The western blot in H358 (KRAS G12C) shows at 24 hours of treatment that either selinexor or selinexor plus tepotinib inhibits XPO1, as well as SOX2 (cancer stem cell marker) that can be upregulated through YAP activation. MRAS protein remains stable since the KRAS G12C inhibitor has not been used in the experiments. However, the combination of selinexor plus tepotinib shows synergism and, importantly, increases RAF serine 259 phosphorylation, indicating that MRAS is not activated.

The authors have no conflicts of interest to declare

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