Assessing replication stress as an actionable therapeutic opportunity in chordoma
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ABSTRACT

• Tumor genomics profiling and functional genomics studies have identified replication stress as a potential therapeutic vulnerability in chordoma, which is a rare type of bone cancer with no approved systemic therapies.
• We demonstrate that preclinical models of chordoma exhibit a replication stress phenotype and dependence on ATR activity – particularly when replication stress is exacerbated pharmacologically by ATR inhibition or gemcitabine.
• A panel of 14 chordoma cell lines were treated with the ATR inhibitor (ATRi) elimusertib (BAY1895344) or gemcitabine. Chordoma cells displayed differential sensitivity to elimusertib, with 9 of 14 cell lines having Absolute EC50 values below 100 nM. Chordoma cells are highly sensitive to gemcitabine, with Absolute EC50s below 100 nM in all 14 cell lines and less than 10 nM in 9 of 14 lines.
• Untreated ATRi- and gemcitabine-sensitive cells are characterized by an ongoing replication stress response and double-stranded DNA breaks at baseline.
• DNA fiber assays indicate that ATR causes a mild decrease in replication fork speed and a significant increase in fork asymmetry in ATRi-sensitive cells, suggesting possible fork stalling or collapse. This is supported by flow cytometry, which indicates that ATRi or gemcitabine promote replication catastrophe.
• ATR and gemcitabine are highly active in several chordoma PDX models, in some cases producing tumor regressions and complete responses.
• ATR and gemcitabine synergistically reduce viability of chordoma cell lines.

BACKGROUND

• Chordoma is a rare bone cancer of the skull base and spine that arises from remnants of the embryonic notochord.
• Disease incidence is 1 per million, with median survival from diagnosis of 8 years.
• Standard care is surgical resection +/- radiation, which cures ~30% of patients.
• Chordoma is a relentless disease with a high rate of recurrence; most patients experience serial recurrences with progressively shorter disease-free intervals.
• There are no approved systemic therapies for the treatment of chordoma, motivating the search for effective strategies.
• Chordomas exhibit frequent alterations in DNA damage repair or SWI/SNF chromatin remodeling genes, which have been associated with replication stress.
• Many chordomas are characterized by genomic signatures indicative of defective homologous recombination repair (S. GROSCHL et al., Nat Commun, 2019), which may create a vulnerability to replication stress.
• Replication stress response genes DSSC1 and FANCIC are selectively expressed in chordoma cell lines (T. SHARFINI et al., Nat Commun, 2023).

RESULTS

• Chordoma cells are sensitive to therapies that promote replication stress.

KEY FINDINGS AND NEXT STEPS

• Our data reveal that a subset of chordomas are sensitive to therapeutic agents that promote replication stress, including ATR inhibitors and gemcitabine.
• Chordoma cells appear to be highly sensitive to gemcitabine, which induces complete tumor responses in a subset of chordoma PDX models.
• ATR inhibitors or gemcitabine promote replication catastrophe and lethal DNA damage, particularly in cells with pre-existing replication stress or unresolved double-stranded DNA breaks.
• ATR and gemcitabine synergistically reduce cell viability in chordoma cell lines. Continuing efforts will focus on identifying synergistic combination therapies that further enhance the magnitude and duration of antitumor response.
• Bioinformatics analysis is ongoing to identify molecular features that predict response to ATR inhibitors or gemcitabine.