Targeting Ribosome Biogenesis in Cancer: Current Insights

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Ribosome biogenesis (RiBi) inhibition has emerged as a semi-specific therapeutic strategy in cancer treatment. In support, there is experimental and clinical evidence collected from a few cancer types. Our research explores small molecules targeting RiBi, first highlighting the novel activity of the FDA-approved antimalarial drug amodiaquine. Screening a drug library of FDA approved compounds, we discovered that amodiaquine inhibits rRNA transcription and degrades the RNA polymerase I catalytic subunit, with mechanistic similarities to BMH-21, a RiBi inhibitor, suggesting its potential for cancer therapy repurposing. Furthermore, in high-grade gliomas, a positive correlation between RiBi activity and tumor aggressiveness was identified through transcriptomic data analysis. We tested a panel of RiBi inhibitors, and BMH-21, reduced glioma cell viability, induced apoptosis, and impaired tumor growth in zebrafish models effectively. A small molecule synergy screen conducted using BMH-21 identified FGFR inhibitors, particularly Erdafitinib as a promising combinatorial approach. Indeed, resistance to chemotherapy, irradiation in glioma is often mediated through FGFR1-FGF2 signaling. A current problem with RiBi inhibitors is that they are not truly specific for RNA pol I and several of them intercalate into DNA. Hence, we could show that although DNA intercalators like BMH-21, Aclarubicin, and Curaxin CBL0137 are highly effective inhibitors of RNA pol I transcription and induces nucleolar stress, these compounds also exhibit broader cytotoxic effects by disrupting chromatin stability yet without inducing DNA damage. These compounds dissociate RNA polymerases I-III from chromatin, trap topoisomerases on chromatin, impacting transcription machinery and chromatin homeostasis. Further mechanistic insights regarding these non-DNA damaging compounds as seen from our recent chromatome analysis will be discussed with specific emphasis on nucleolar chromatin and rDNA transcription.

References

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