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9-Aminoacridine Inhibits Ribosome Biogenesis and Synergizes with Cytotoxic Drugs to Induce Selective Killing of p53-Deficient Cells

Leonid Anikin
Rowan University

Dimitri G Pestov
Rowan University

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9-Aminoacridine inhibits ribosome biogenesis and synergizes with cytotoxic drugs to induce selective killing of p53-deficient cells.

L. Anikin[1,2], D. Pestov[1];
[1]Cell Biology Neuroscience, Rowan University School of Osteopathic Medicine, Stratford, NJ, [2]Graduate School of Biomedical Sciences, Rowan University, Stratford, NJ

Common cancer treatments target rapidly dividing cells and do not discriminate between cancer and normal host cells. One approach to mitigating negative side-effects of cancer treatment is to temporarily arrest cell cycle progression and thus protect normal cells during cytotoxic treatments, a concept called cyclotherapy. We recently proposed that transient inhibition of post-transcriptional steps of ribosome biogenesis (RBG) can be used to selectively arrest p53-positive host cells and not p53-null cancer cells. In this study, we investigated whether cytoprotective RBG inhibition can be achieved through small

molecule treatment. We report that treatment of cells with 9-aminoacridine (9-AA) inhibits pre-rRNA processing as well as RNA Polymerase I (Pol I) transcription, in a dose-dependent manner. We propose a mechanism for 9-AA inhibition of RBG by disruption of binding between pre-ribosomes and small nucleolar RNAs (snoRNAs) required for rRNA maturation. Our data also indicate that the mechanism of Pol I inhibition by 9-AA is distinct from that of actinomycin D (Act D), an established Pol I inhibitor. We demonstrate in a model 3T3 cell system that low doses of 9-AA that reversibly inhibit RBG can be protective for p53-positive cells and used in synergy with anti-cancer agents camptothecin and methotrexate to selectively kill p53-negative cells. The ability of 9-AA to cause RBG inhibition, as well as the decoupling of the inhibition of Pol I transcription and pre-rRNA processing, positions acridines as a new tool for RBG and cyclotherapy research.