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## Nucleic acid consequences of targeting mitochondrial RNA polymerase as an anticancer therapeutic strategy

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One of the hallmarks of cancer is dysregulated metabolism. A subset of many cancers possess unique mitochondrial characteristics such as increased mitochondrial mass and mitochondrial DNA, a higher reliance on oxidative phosphorylation (OXPHOS) and a lower spare reserve capacity compared to their normal counterparts. We focused on a novel non-mutant therapeutic target, the mitochondrial RNA polymerase (POLRMT) which indirectly controls oxidative phosphorylation (OXPHOS) by transcribing 13 essential subunits of the mitochondrial electron transport chain. While mitochondria are ubiquitous in all cells, their unique dysregulation in some cancer cells and heightened response to POLRMT depletion indicates a real possibility for anti-cancer therapy. This study focused on acute myeloid leukemia as one type of cancer with a high reliance on OXPHOS. Using the ribonucleoside analogue 4'-azidocytidine, a chain terminator of mitochondrial transcription, we observed that 4'-azidocytidine decreased growth and viability of leukemia and lymphoma cell lines. An unanticipated finding was that, paradoxically, 4'-azidocytidine increases nascent mitochondrial gene expression at short timepoints. Since POLRMT also acts as a primase for mitochondrial DNA replication, we asked whether mitochondrial DNA levels were affected by 4'-azidocytidine, but it did not alter mitochondrial DNA abundance. Our interpretation of the elevation in nascent mitochondrial RNA was that cancer cells stabilize mitochondrial RNA to prevent its degradation. Using genome-wide RNA-sequencing, we observed that 4'-azidocytidine decreased total mitochondrial gene expression while the expression of nuclear genes was generally unaffected, with the exception of a specific increase in the expression of nuclear genes encoding mitochondrial electron transport chain subunits, likely as a compensatory response. 4'-azidocytidine decreased the levels of mitochondrial DNA-encoded protein subunits, and inhibited mitochondrial respiration in leukemia cell lines. We treated primary AML patient samples and observed a heterogeneous mitochondrial gene expression response to 4'-azidocytidine.

### Biography

Rebecca Laposa has a strong interest in mitochondrial toxicity and mitochondrial drug delivery, particularly in cancer therapeutic strategies. She has interest and experience in translational pharmacology research with a focus towards drug development. At the level of the molecular biology of nucleic acids, she is interested in DNA and RNA damage, and DNA and RNA responses to those molecular insults.

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