JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue

JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)

An International Scholarly Open Access, Peer-reviewed, Refereed Journal

An Analysis and Future Outlook on Repositioning Ribavirin as a Multi-Target Anticancer Agent

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Abstract

Drug repurposing offers a promising pathway to accelerate the development of cancer therapeutics by leveraging existing pharmacological and safety data. Ribavirin, a nucleoside analogue traditionally used as an antiviral agent, has recently attracted interest for its potential anticancer properties. A pivotal 2015 investigation by De La Cruz-Hernandez and colleagues suggested a novel triple-target mechanism, proposing that ribavirin inhibits eIF4E, IMPDH, and—for the first time—the epigenetic regulator EZH2. This review offers a detailed critique of that foundational work, recognizing its innovative use of computational methods to identify EZH2 as a target and its validation of a multi-target mode of action. At the same time, the review highlights several methodological shortcomings, including insufficient evidence of direct EZH2 binding, a lack of in vivo confirmation, and inadequate analysis of differential cellular responses. To bridge these gaps, we propose a forward-looking research agenda focused on mechanistic validation, rational combination therapies, biomarker identification, and rigorous preclinical models to facilitate the clinical translation of ribavirin as an oncology treatment.

Keywords: Ribavirin, Anticancer Drug Repurposing, eIF4E, IMPDH, EZH2, Epigenetic Therapy, Multi-Target Inhibition

1. Introduction

The journey from drug discovery to clinical application in oncology is often long, costly, and fraught with failure. Repurposing existing drugs for new therapeutic uses presents a viable alternative, capitalizing on established safety profiles and known pharmacokinetics to shorten development timelines (Hernandez et al., 2017). Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide), a synthetic guanosine analogue, has been widely used for decades to treat viral infections such as hepatitis C and respiratory syncytial virus (Sidwell et al., 1972; Reichard et al., 1991), making it a strong candidate for repurposing.

Interest in ribavirin's anticancer effects emerged following its identification as an inhibitor of eukaryotic translation initiation factor 4E (eIF4E), an oncogenic protein overexpressed in many cancers and linked to aggressive disease and poor outcomes (Kentsis et al., 2004; Borden & Culjkovic-Kraljacic, 2010). Early-phase clinical trials in acute myeloid leukemia (AML) patients with elevated eIF4E levels provided preliminary evidence of its efficacy (Assouline et al., 2009). Additionally, ribavirin's capacity to inhibit inosine-5′-monophosphate dehydrogenase (IMPDH), an enzyme critical for guanine nucleotide biosynthesis in rapidly dividing cells, further supported its potential role in cancer treatment (Chen & Pankiewicz, 2007).

A significant expansion of ribavirin's proposed mechanism came in 2015, when De La Cruz-Hernandez et al. put forth evidence that it also targets enhancer of zeste homolog 2 (EZH2), a histone methyltransferase involved in epigenetic regulation and frequently altered in cancers. This triple-target hypothesis positioned ribavirin as a multi-functional agent with broad anticancer potential. This review critically evaluates that landmark study, acknowledging its contributions while addressing its limitations, and suggests a roadmap for future research to realize ribavirin's promise in oncology.

Application

- Respiratory viral infections
- Chronic hepatitis C virus infection
- Viral hemorrhagic fevers(VHFs)
- As a resistant for viral infections in immunocompromised patients
- As an anti-tumor drug

2. Evaluation and Limitations

2.1. Insufficient Evidence for Direct EZH2 Engagement

The most notable shortcoming is the lack of direct evidence that ribavirin binds to and inhibits EZH2. The argument rests largely on correlative data: structural resemblance to DZNep, reduced EZH2 expression, and decreased H3K27me3.

Limitation: Changes in EZH2 expression and activity may be secondary to other effects, such as general translational suppression via eIF4E inhibition or cellular stress responses. Since DZNep inhibits EZH2 indirectly via S-adenosylhomocysteine hydrolase (SAHH) inhibition, it remains unclear whether ribavirin

shares this mechanism or binds EZH2 directly. Direct enzymatic assays with recombinant EZH2 are necessary to confirm inhibition.

2.2. Narrow Epigenetic Characterization

The epigenetic analysis was restricted to only three histone marks.

Limitation: A more comprehensive profiling—using techniques such as ChIP-seq or mass spectrometry—would provide a global view of ribavirin's epigenetic influence and help ascertain its specificity for EZH2-mediated silencing. Moreover, the cell-type-specific effects on EZH2 were not explained mechanistically (e.g., differences in EZH2 mutational status, expression levels, or cellular background).

2.3. Lack of In Vivo Corroboration

The study was confined to cell-based models.

Limitation: In vivo validation is essential to evaluate pharmacokinetics, biodistribution, tumor penetration, and efficacy within a physiologic microenvironment. Although ribavirin plasma concentrations in clinical AML studies (5–36 μM; Assouline et al., 2009) overlap with effective in vitro doses, tumor tissue concentrations and EZH2 inhibition in vivo remain unverified.

2.4. Incomplete Interrogation of Cell-Type Specificity

Responses to ribavirin varied widely across cell lines, and epigenetic effects were inconsistent.

Limitation: The authors did not correlate sensitivity with baseline expression or activation of eIF4E, IMPDH, or EZH2. Understanding the determinants of response is critical for patient selection. For example, the absence of EZH2 modulation in D54 cells—despite robust growth inhibition—suggests that in this context, ribavirin acts mainly through eIF4E and IMPDH.

2.5. Unclear Clinical Development Strategy

The study recommends further investigation but does not outline a translational plan.

Limitation: The optimal cancer types for ribavirin therapy—either as monotherapy or in combination—remain undefined. Furthermore, the potential dose-limiting toxicity of hemolytic anemia, well-documented during antiviral use (Russmann et al., 2006), was not discussed in the context of chronic cancer treatment.

3. Recommended Research Directions

3.1. Mechanistic Validation of EZH2 Targeting

Approach: Apply direct binding assays (e.g., surface plasmon resonance, isothermal titration calorimetry) using purified EZH2 protein and ribavirin or its metabolites.

Approach: Implement cellular thermal shift assays (CETSA) to probe target engagement in live cells.

Approach: Determine whether ribavirin affects methyl donor metabolism by quantifying intracellular S-adenosylhomocysteine (SAH) and S-adenosylmethionine (SAM) levels.

3.2. Rigorous Preclinical In Vivo Evaluation

Approach: Employ patient-derived xenograft (PDX) models or genetically engineered mouse models (GEMMs) of cancers with documented eIF4E, IMPDH, or EZH2 dysregulation.

Approach: Conduct pharmacodynamic studies in tumor tissues to verify target modulation (e.g., diminished eIF4E cap-binding, reduced GTP levels, decreased H3K27me3).

3.3. Biomarker-Driven Patient Selection

Approach: Develop predictive biomarkers based on tumor expression and activation status of eIF4E, IMPDH isoforms, and EZH2.

Approach: Re-analyze existing cell-line data to correlate molecular features with ribavirin sensitivity and generate testable biomarker hypotheses.

3.4. Rational Combination Strategies

Since ribavirin may be primarily cytostatic, combinations are likely necessary.

Approach: Combine with conventional chemotherapy (e.g., cytarabine in AML) or targeted agents (e.g., EZH2-specific inhibitors like tazemetostat) to overcome compensatory resistance.

Approach: Explore synergies with immunotherapies, leveraging ribavirin's immunomodulatory properties (e.g., Th1/Th2 shift; Kast, 2002) to enhance checkpoint inhibitor efficacy.

3.5. Toxicity Management

Approach: Test intermittent dosing or lower doses in combination regimens to reduce hemolytic anemia.

Approach: Incorporate supportive care strategies, such as erythropoietin, to manage anemia during treatment.

4. Conclusion

The study by the scientist meaningfully advanced the field by proposing EZH2 inhibition as a new mechanism underpinning ribavirin's anticancer effects. Its use of in silico methods to identify a novel target is especially noteworthy. However, clinical translation requires overcoming several key limitations—particularly the lack of direct EZH2 binding evidence and in vivo proof of concept.

Future work must adopt a more comprehensive and mechanistic approach to validate ribavirin's targets, define responsive patient subsets, and develop rational combination regimens. If these challenges are met, ribavirin could transition from a broad-spectrum antiviral to a targeted anticancer agent, underscoring the strategic value of drug repurposing in oncology. Rather than a standalone therapy, its greatest potential may lie as part of a multi-targeted treatment strategy.

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