Miricorilant, a Selective Glucocorticoid Receptor Modulator, Reprograms Hepatic Gene Networks in Metabolic Dysfunction–Associated Steatohepatitis

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Poster 1457

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CONCLUSIONS

- Miricorilant selectively modulated key genes in pathways regulating hepatic steatosis, metabolism, oxidative stress, inflammation, and fibrosis
  - Early response (8 h exposure) was characterized by upregulation of genes associated with lipid metabolism, detoxification, and cellular stress responses, indicating enhanced hepatic metabolic function and immediate protection against oxidative and inflammatory stress
  - Sub-chronic response (5 d exposure) was characterized by sustained upregulation of lipid metabolism regulators and downregulation of gluconeogenic enzymes, supporting long-term improvements in hepatic steatosis, insulin sensitivity, and potentially fibrosis
- Collectively, these results highlight the potential of miricorilant as a liver-targeted therapy for MASH as it operates through the selective and time-dependent modulation of key pathophysiological processes
- The ongoing phase 2b MONARCH trial (NCT06108219) is currently evaluating miricorilant in patients with biopsy-confirmed or presumed noncirrhotic MASH

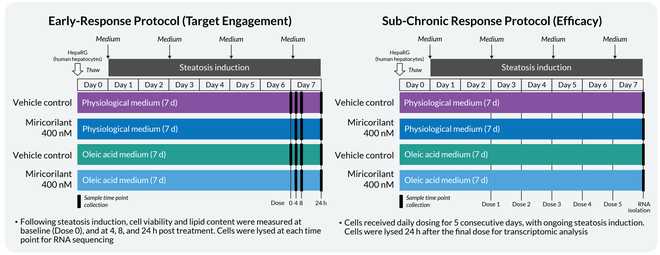
BACKGROUND AND OBJECTIVE

- Cortisol has been implicated in the development and progression of MASLD[1,2]
  - Through GR activation, cortisol promotes the mobilization of energy substrates, such as FAs, to support circadian activity and stress adaptation
  - Chronic or dysregulated cortisol signaling can contribute to hepatic lipid accumulation by enhancing FA uptake, reducing FA beta-oxidation, and stimulating de novo lipogenesis[3]
- Miricorilant is an oral, selective GR modulator that acts as a mixed GR agonist/antagonist and modest mineralocorticoid receptor antagonist
- Miricorilant exhibits preferential distribution to the liver, making it a promising candidate for modulating hepatic glucocorticoid activity
  - In preclinical models of MASLD/MASH, miricorilant both prevented and reversed hepatic steatosis, reduced inflammation, and improved fibrosis and NAS[4]
- In a phase 1b study (NCT05117489) in adults with presumed MASH and fibrosis, miricorilant treatment reduced liver fat content by a mean of 28.2% and improved hepatic, lipid, and glycemic biomarkers[5]
- Understanding the transcriptional regulation of hepatocytes in response to miricorilant is essential for elucidating its mechanism of action
- The objective of this study was to assess the effects of miricorilant on gene expression in vitro in human hepatocyte-like cells under simulated physiological and steatotic conditions

METHODS

- Transcriptomic analysis was performed using an in vitro MASH model with HepaRG™ cells, a human bipotent progenitor cell line capable of differentiating into hepatocyte-like cells. Cells were cultured for 7 d in either physiological or oleic acid–enriched (250 µM oleic acid diluted 1:400 in methanol) medium and treated with vehicle or miricorilant 400 nM under 2 experimental timelines (**Figure 1**)
  - Culturing in oleic acid–enriched medium resulted in the accumulation of lipids as measured by Oil Red O staining, mimicking the effect of fatty liver

Figure 1. In Vitro MASH Model Design and Study Experimental Timelines



- Following steatosis induction, cell viability and lipid content were measured at baseline (Dose 0), and at 4, 8, and 24 h post treatment. Cells were lysed at each time point for RNA sequencing
- Cells received daily dosing for 5 consecutive days, with ongoing steatosis induction. Cells were lysed 24 h after the final dose for transcriptomic analysis

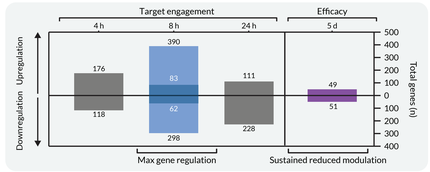
- RNA was extracted from lysed cells and pre-analysis of RNAseq data was processed using the Rosalind cloud-based genomics platform,[6] which identified 19,912 unique transcripts across 54 samples
- For clustering and principal component analysis, count data were transformed using $\log_2$ (CPM+4), applying a minimum threshold of 0.5 CPM across all samples
- DGE analysis was performed using the Limma-Voom method, with a false discovery rate cutoff of 0.1 and a minimum fold change of 1.0, with 12,236 genes passing the filter criteria
- STRING, a protein-protein interaction networks functional enrichment analysis web tool, was used to identify biological pathways significantly associated with the differentially expressed genes[7]
- Statistical analysis of early response and sub-chronic phases employed 2-way ANOVA. Comparisons included treatment effects and media conditions

RESULTS

Time-Dependent Therapeutic Modulation of Hepatic Metabolism

- Analysis of miricorilant treatment under steatotic conditions revealed rapid and time-dependent therapeutic effects (**Figure 2**)

Figure 2. Miricorilant Transcription Regulation vs Vehicle Under Steatotic Conditions

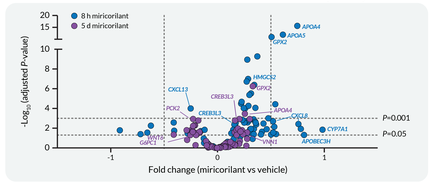


- Within 8 h, miricorilant induced significant DGE compared with the other three conditions, upregulating 390 genes and downregulating 298
  - Among the upregulated genes, 83 (21.3%) were associated with lipid metabolic processes (including steroid, cholesterol, and FA processes)
  - 62 (20.8%) of the downregulated genes were linked to cell cycle processes (including chromosome segregation and cell division)
- This rapid shift was confirmed by a separate, statistically stringent analysis (adjusted $P \leq 0.05$; $|FC| \geq 0.25$) of the effect of miricorilant after 8 h, which identified 72 upregulated genes tied to lipid metabolism and 25 downregulated genes associated with the cell cycle
- After 5 d of treatment with miricorilant, upregulation of lipid metabolism regulators was maintained at a lower level, whereas genes related to glucose production were downregulated

Genes Modulated by Miricorilant: Early and Sub-Chronic Responses

- To characterize the transcriptomic response to miricorilant under steatotic conditions, we conducted a comparative analysis across the early response phase and the sub-chronic phase to capture both initial and sustained effects
- Differential expression analysis (adjusted $P \leq 0.05$; $|FC| \geq 0.15$) identified 459 genes whose regulation was highly time dependent, as most (83%) were unique to a single time point
- From this dataset, we selected a focused panel of 87 biologically relevant genes for deeper study (**Figure 3**)

Figure 3. Fold Change in Gene Expression Between Miricorilant and Vehicle Under Steatotic Conditions for Selected Genes (N=87)

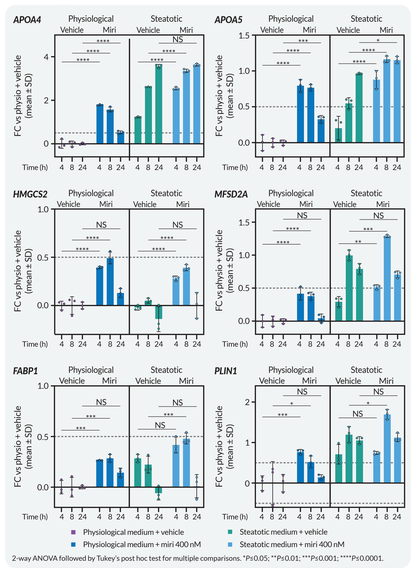


Early Response

Genes Involved in Lipid Metabolism and Transport

- Miricorilant activated a range of genes that enhance lipid metabolism and export, including *APOA4* and *APOA5*, which promote triglyceride secretion and regulate lipid transport out of the liver
- Miricorilant also induced *HMGCS2*, indicating a shift in liver metabolism toward FA oxidation and ketogenesis
- Miricorilant transiently modulated other lipid-related genes like *MFSD2A*, *FABP1*, and *PLIN1* (**Figure 4**)

Figure 4. Expression of Genes Associated With Lipid Metabolism and Transport

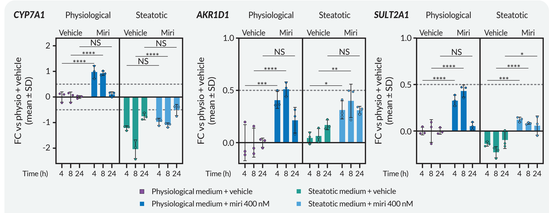


2-way ANOVA followed by Tukey's post hoc test for multiple comparisons. *P≤0.05; **P≤0.01; ***P≤0.001; ****P≤0.0001.

Genes Regulating Bile Acid Homeostasis

- Miricorilant may promote cholesterol elimination, reduce toxic bile acid accumulation, and modulate hepatic lipid content, potentially mitigating liver inflammation and fibrosis, as suggested by changes in gene expression
  - Miricorilant promoted the expression of *CYP7A1*, the gene that codes for the rate-limiting enzyme for bile acid synthesis from cholesterol, and induced *AKR1D1* expression, which is essential for proper bile acid synthesis and prevention of lipid accumulation
  - Miricorilant also induced *SULT2A1* expression, a gene critical for bile acid detoxification (**Figure 5**)

Figure 5. Expression of Genes Important for Bile Acid Homeostasis

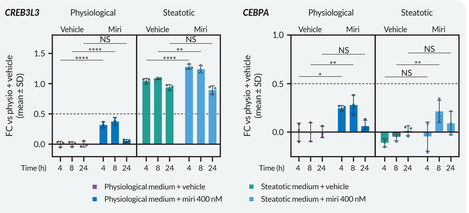


2-way ANOVA followed by Tukey's post hoc test for multiple comparisons. *P≤0.05; **P≤0.01; ***P≤0.001; ****P≤0.0001.

Transcription Factors

- Miricorilant modulated the expression of transcription factors *CREB3L3* and *CEBPA* (**Figure 6**)
  - CREB3L3 promotes FA oxidation, reduces liver fat accumulation, inhibits de novo lipogenesis, suppresses lipid synthesis, regulates the acute phase response, and induces protective hepatokines
  - CEBPA maintains healthy hepatocyte function, regulates lipid metabolism, and suppresses pro-fibrotic and inflammatory pathways
  - Loss of *CEBPA* is linked to increased liver fibrosis and worse MASH outcomes; upregulation protects against these changes

Figure 6. Expression of *CREB3L3* and *CEBPA*

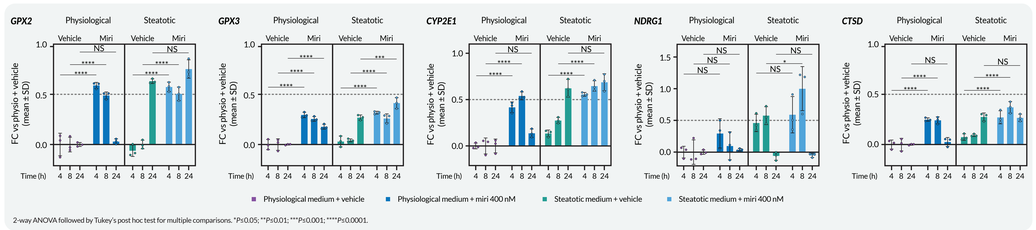


2-way ANOVA followed by Tukey's post hoc test for multiple comparisons. *P≤0.05; **P≤0.01; ***P≤0.001; ****P≤0.0001.

Other Genes

- Miricorilant upregulated expression of genes that code for antioxidant enzymes and genes associated with stress response (**Figure 7**)
- Miricorilant also upregulated *CXCL8* and downregulated *CXCL13*, which play a role in hepatocyte pathways for immune cell recruitment (data not shown)

Figure 7. Expression of Genes Involved in Antioxidant/Detoxification Systems and Stress Response



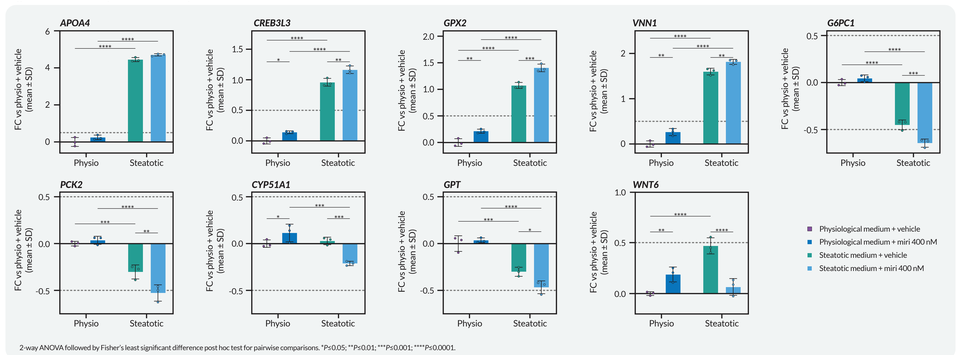
2-way ANOVA followed by Tukey's post hoc test for multiple comparisons. *P≤0.05; **P≤0.01; ***P≤0.001; ****P≤0.0001.

Sub-Chronic Response

Genes Involved in Adaptive Responses in Liver Metabolism and Cellular Protection

- Categories of genes regulated by miricorilant after 5 d of treatment (**Figure 8**) included:
  - Genes associated with lipid handling and antioxidant defense
    - Upregulated *APOA4*, which promotes lipid export and reduced liver fat
    - Upregulated *CREB3L3*, which supports triglyceride homeostasis and endoplasmic reticulum stress management
    - Upregulated *GPX2*, a gene associated with antioxidant defenses against inflammation and fibrosis
    - Sustained upregulation in *VNN1*, which impacts redox balance and metabolic pathways
  - Genes associated with glucose production and metabolic flux
    - Downregulated *G6PC1* and *PCK2*, which code for key gluconeogenic enzymes
    - Downregulated *CYP51A1*, which plays a role in cholesterol synthesis
    - Downregulated *GPT*, which codes for a key enzyme in amino acid and intermediary metabolism
  - Genes involved with cellular protection and tissue response
    - Downregulated *WNT6*, which modulates cell growth and differentiation pathways
- Expression of the gene coding for the GR (*NR3C1*) was detected across media and did not change with medium or treatment (data not shown)

Figure 8. Gene Expression Analysis After 5 d of Treatment



2-way ANOVA followed by Fisher's least significant difference post hoc test for pairwise comparisons. *P≤0.05; **P≤0.01; ***P≤0.001; ****P≤0.0001.

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Presenter Disclosures

Disclosure of relevant financial relationships for all authors: RMM, HJH, AE, WG, and KJ are employed by and own stock in Corcept; JK is employed by Corcept.

Abbreviations

AKR, aldo-keto reductase; ANOVA, analysis of variance; APOA, apolipoprotein A; APOBEC3H, apolipoprotein B mRNA editing enzyme catalytic subunit 3H; CEBPA, CCAAT/enhancer binding protein alpha; CPM, counts per million; CREB3L3, cyclic AMP-responsive element binding protein 3-like 3; CTSD, cathepsin D; CXCL, C-X-C motif chemokine ligand; CYP, cytochrome P450; d, days; DGE, differential gene expression; FA, fatty acid; FABP, fatty acid binding protein; FC, fold change; G6PC, glucose-6-phosphatase catalytic subunit; GPT, glutamic-pyruvic transaminase; GPX, glutathione peroxidase; GR, glucocorticoid receptor; h, hours; HMGCS, hydroxymethylglutaryl-CoA synthase; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; Max, maximum; MFSD, major facilitator superfamily domain-containing protein; miri, miricorilant; NAS, nonalcoholic fatty liver disease activity score; NDRG, N-myc downstream regulated gene; NR, nuclear receptor subfamily; NS, not significant; PCK, phosphoenolpyruvate carboxykinase; physio, physiological; PLIN, perilipin; RNAseq, RNA sequencing; SD, standard deviation; SULT, sulfotransferase; VNN, vanin; WNT, wingless-type mouse mammary tumor virus integration site.

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