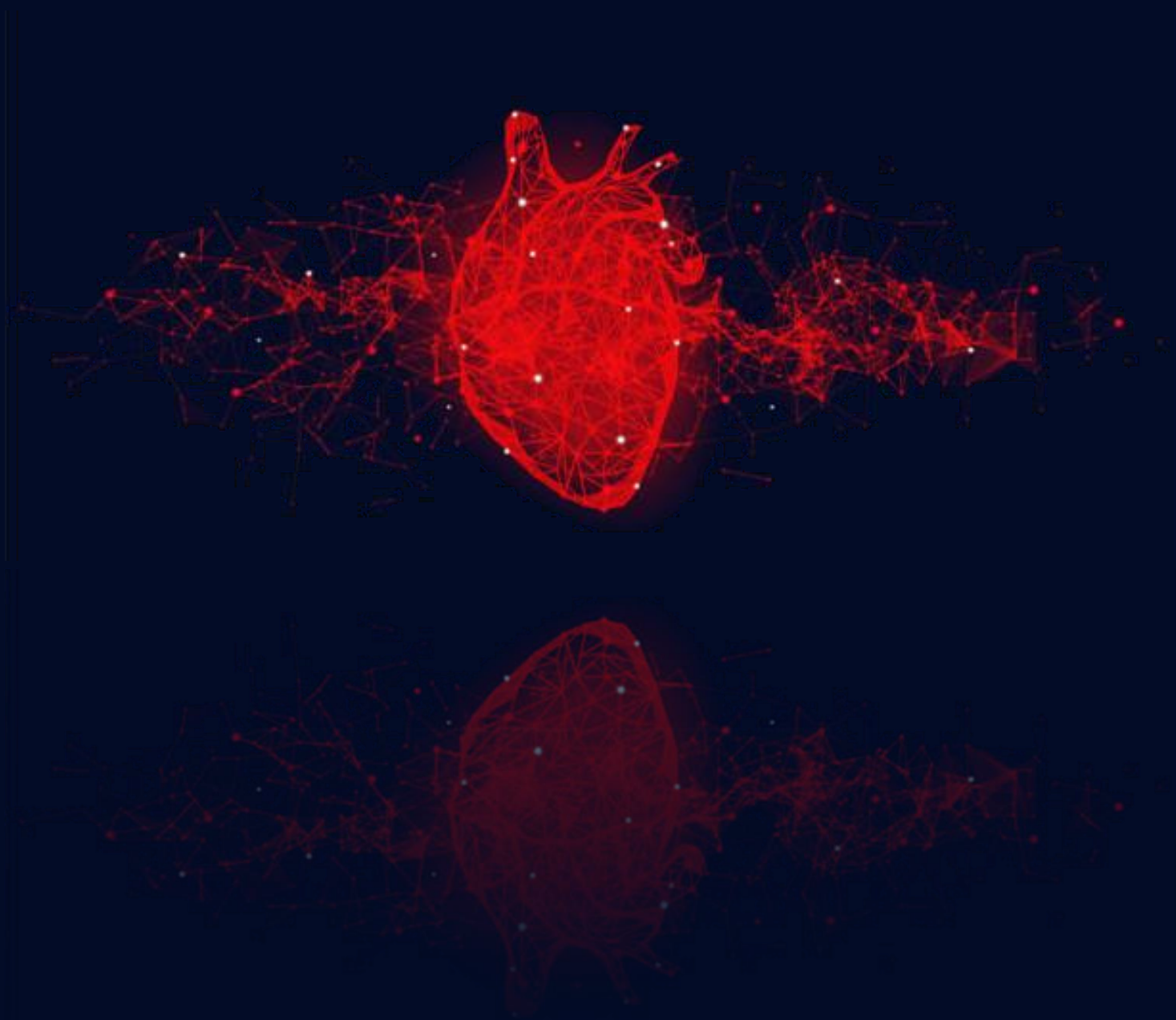
Publications



Publications

Vyas, Hitarthi S., Kapil K. Upadhyay, and Ranjitsinh V. Devkar. "miRNAs Signatures in Patients with Acute Liver Injury: Clinical Concerns and Correlations." *Current Molecular Medicine* 20, no. 5 (2020): 325-335.

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Upadhyay, Kapil K., Ravirajsinh N. Jadeja**, Hitarthi S. Vyas**, Bhaumik Pandya, Apeksha Joshi, Aliasgar Vohra, Menaka C. Thounaojam, Pamela M. Martin, Manuela Bartoli, and Ranjitsinh V. Devkar. "Carbon monoxide releasing molecule-A1 improves nonalcoholic steatohepatitis via Nrf2 activation mediated improvement in oxidative stress and mitochondrial function." *Redox Biology* 28 (2020): 101314.

Publications from collaborations

Nariya, Pratik, Falguni Shukla, **Hitarthi Vyas,** Ranjitsinh Devkar, and Sonal Thakore. "Synthesis, characterization, DNA/BSA binding and cytotoxicity studies of Mononuclear Cu (II) and V (IV) complexes of Mannich bases derived from Lawsone." *Journal of Molecular Structure* 1248 (2022): 131508.

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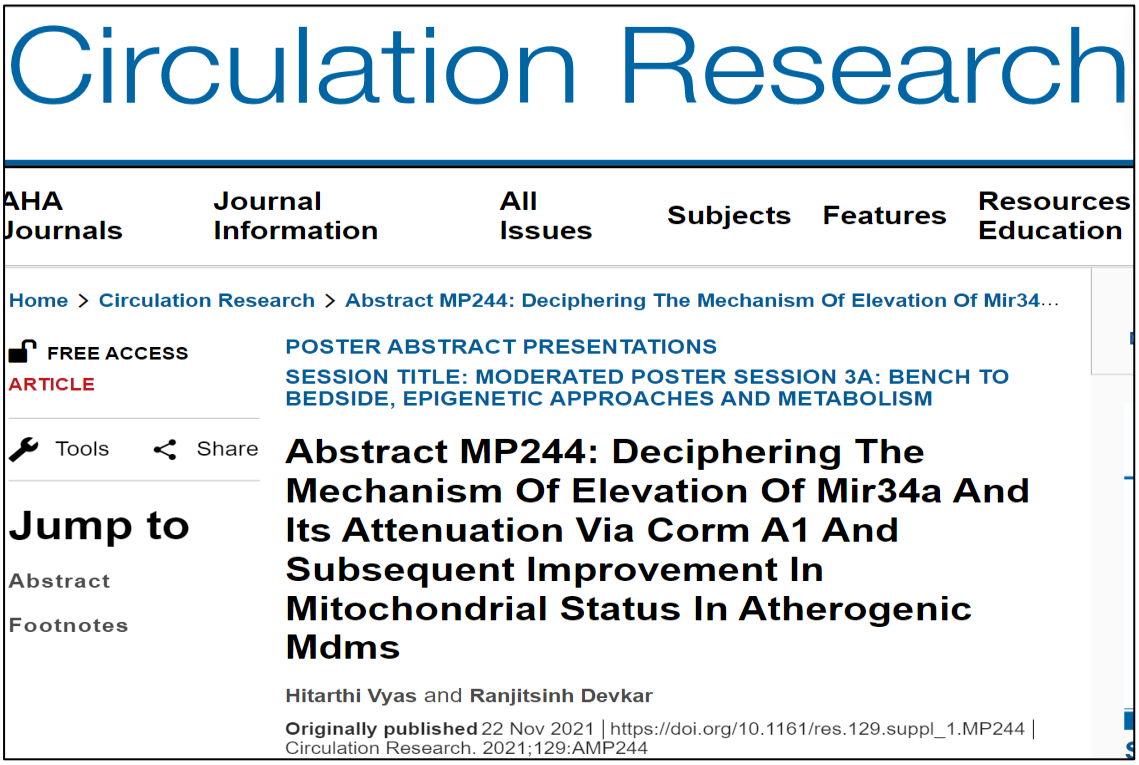

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Hitarthi Vyas and **Ranjitsinh Devkar**

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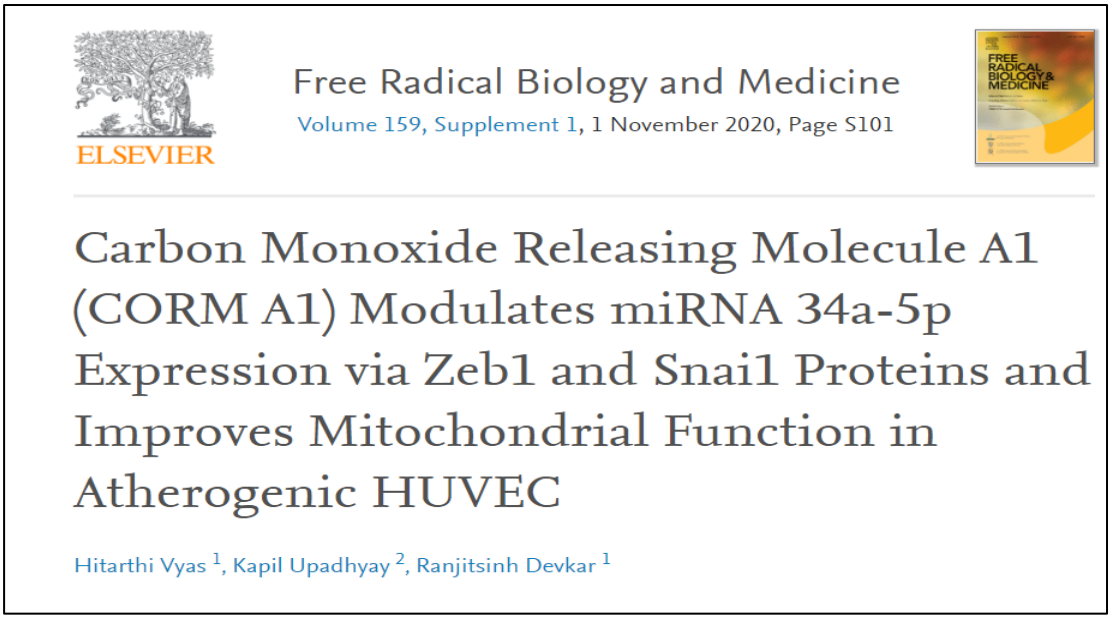

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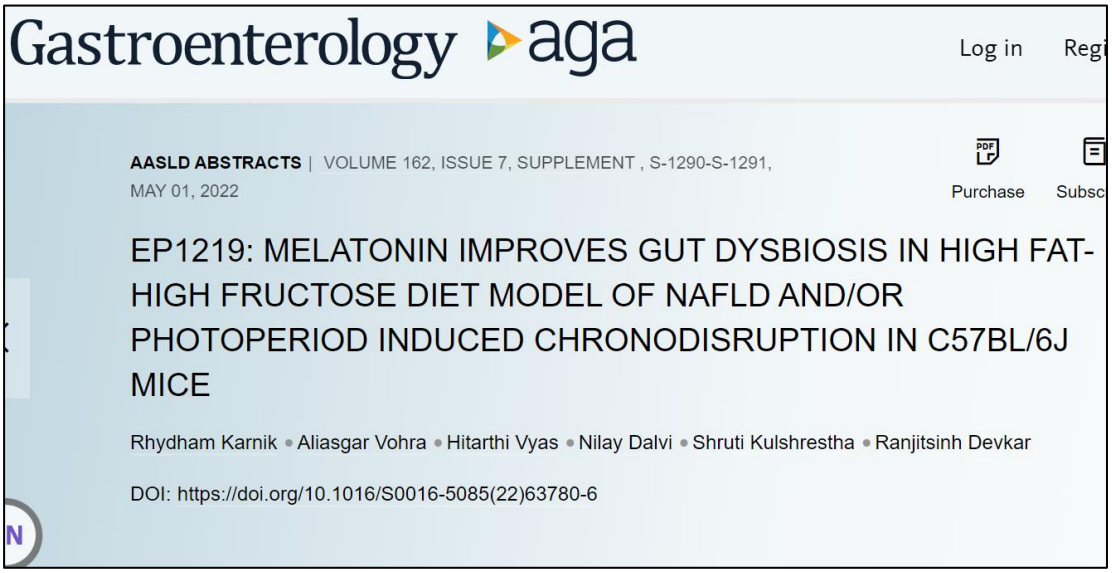
Carbon Monoxide Releasing Molecule A1 (CORM A1) Modulates miRNA 34a-5p Expression via Zeb1 and Snai1 Proteins and Improves Mitochondrial Function in Atherogenic HUVEC

Hitarthi Vyas [1], Kapil Upadhyay [2], Ranjitsinh Devkar [1]



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Rhydham Karnik • Aliasgar Vohra • Hitarthi Vyas • Nilay Dalvi • Shruti Kulshrestha • Ranjitsinh Devkar

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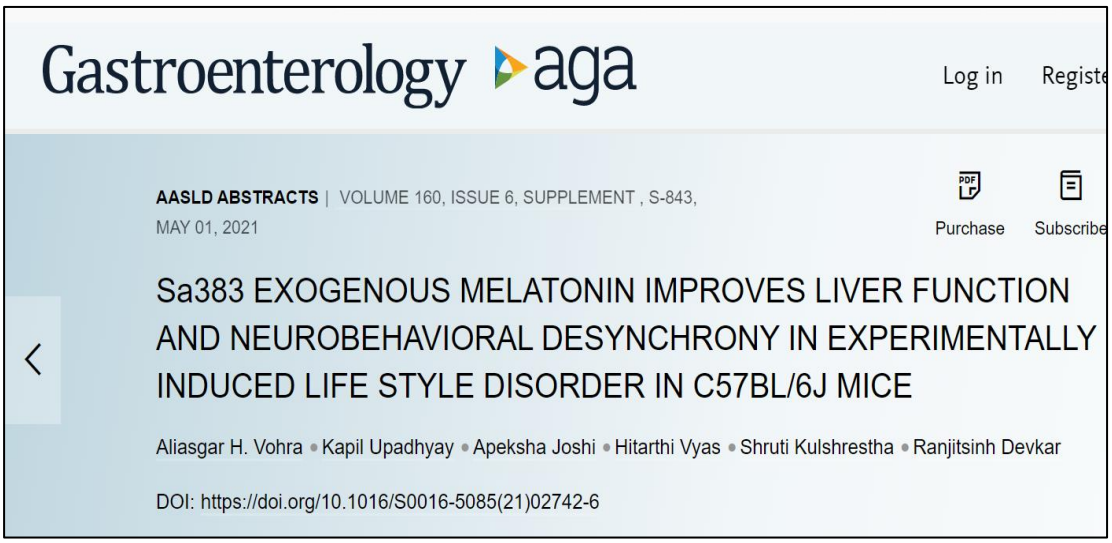

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Sa383 EXOGENOUS MELATONIN IMPROVES LIVER FUNCTION AND NEUROBEHAVIORAL DESYNCHRONY IN EXPERIMENTALLY INDUCED LIFE STYLE DISORDER IN C57BL/6J MICE

Aliasgar H. Vohra • Kapil Upadhyay • Apeksha Joshi • Hitarthi Vyas • Shruti Kulshrestha • Ranjitsinh Devkar

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Mini-REVIEW ARTICLE

miRNAs Signatures in Patients With Acute Liver Injury: Clinical Concerns and Correlations

Hitarthi S. Vyas[a$], Kapil K. Upadhyay[a$] and Ranjitsinh V. Devkar[a,*]

[a]*Division of Metabolic Endocrinology, Department of Zoology, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat 390002, India*

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Abstract: Non-coding RNAs can be highly exploited for their biological significance in living systems. miRNAs are in the upstream position of cellular regulation cascade and hold merit in its state. A plethora of information is available on a wide variety of miRNAs that undergo alterations in experimentally induced models of liver injuries. The underlying mechanisms governed by these miRNAs have been inferred through cell-based experiments but the scientific knowledge on miRNA signatures in patients with liver injury are primordial and lack scientific clarity. Hence, it is crucial to get insight into the status and synergy of miRNAs in patients, with varying degrees of acute toxic manifestations in the liver. Though some miRNAs are being investigated in clinical trials, a major research lacuna exists with regard to the functional role of other miRNAs in liver diseases. This review article is a meticulous compilation of disease based or drug/alcohol based acute liver injuries in patients and resultant alteration in their miRNA profile. Investigative reports on underlying miRNA-liver crosstalk in cell-based or murine models are also discussed herein to draw a correlation with clinical findings.

Keywords: microRNAs, acute liver injury, patients, biomarker.

1. INTRODUCTION

Liver is a vital organ, regulating metabolic processes like blood volume regulation, endocrine controls, lipid, cholesterol and micronutrient metabolism, breaking of xenobiotic components, clearing toxic waste, *etc*. Liver diseases are steadily increasing and attributes for about 2 million deaths per year globally [1]. In the US, liver diseases are recognized as the second leading cause of mortality along with cirrhosis ranking as the 11th most common cause of death globally [2]. These statistics add value in exploring new therapeutic and clinical interventions along with modifying the existing treatment regimens. Liver injuries encountered in clinical practice are broadly classified as acute or chronic liver injuries, based on the duration or persistence. Acute liver injuries are marked by degeneration and necrosis of the liver on exposure to an insult. Acute insults are mostly surmountable with rapid resolution upon the elimination of the injurious agent. Complete restitution of normal histoarchitecture and function can be observed in the case of acute liver injuries. On contrary, the chronic liver diseases are marked by gradual liver damage over a period of time. Progressive fibrosis is the hallmark of chronic liver injury and can eventually result in cirrhosis, liver failure or hepatocellular carcinoma (HCC). Alcoholic abuse, hepatitis virus infections, autoimmune responses, sepsis and drug/chemical induced liver damage are major causative agents orchestrating liver injury. Liver as an organ has an ability of regeneration but the same gets compromised on the bases of type and intensity of abuse. There are several reported therapeutants for treating liver injuries, but people are now venturing into more specific and target orientated therapeutic approaches [3]. Hence, non-coding RNAs like lnc RNA, piRNA and miRNA are being explored as a possible therapeutants and/or biomarkers in several pathological conditions including atherosclerosis, chronic and acute liver injury, Polycystic ovarian syndrome (PCOS), neurodegenerative diseases, kidney dysfunctions, cancers, *etc*. [4-6]. Though the synergy of miRNAs with other events in a disease is not fully deciphered, their dynamics during toxic manifestations and their critical role in the progression of said events are well-acclaimed which make them a tangible target in therapy and a plausible biomarker.

microRNAs (miRNAs) are noncoding endogenously transcribed RNAs that undergo a series of processing to generate short single-stranded (20-22 nucleotide) RNA fragments. miRNA transcription initiates with RNA polymerase II and RNA polymerase III. The majority of the miRNAs currently known are intragenic *i.e*. they are processed from the introns of the coding genes.

*Address correspondence to this author at the Division of Metabolic Endocrinology, Department of Zoology, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat 390002, India; Tel: +91-9825935445; E-mail: rv.devkar-zoo@msubaroda.ac.in
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Egyptian Liver Journal

ORIGINAL RESEARCH ARTICLE Open Access

Melatonin-primed ADMSCs elicit an efficacious therapeutic response in improving high-fat diet induced non-alcoholic fatty liver disease in C57BL/6J mice

Aliasgar Hatimbhai Vohra[1], Kapil Kumar Upadhyay[2], Apeksha Suhas Joshi[1], Hitarthi Swetang Vyas[1], Jaymesh Thadani[3] and Ranjitsinh Vijaysinh Devkar[1*]

Abstract

Background: Stem cells are widely used for therapy including treatment of liver damage. Adipose-derived mesenchymal stem cells (ADMSCs) administered to treat fatty liver are known to improve liver function but their use is restricted due to a poor success rate. This study investigates efficacy of melatonin-primed ADMSCs (Mel. MSCs) in experimentally induced non-alcoholic fatty liver disease (NAFLD).

Results: MSCs treated with LPS showed prominent DCFDA fluorescence as compared to the untreated cells. Also, the JC-1 staining had accounted for higher intensity of green monomer and a weak fluorescence of red dimer indicating weaker mitochondrial membrane potential. But melatonin co-treatment could make necessary corrective changes as evidenced by reverse set of results. The overall cell survival was also found to be improved following melatonin treatment as evidenced by the MTT assay. Also, the antioxidant (*Nrf2* and *Ho-1*) and anti-inflammatory genes (*Il-4* and *Il-10*) showed a decrement in their mRNA levels following LPS treatment whereas the pro-inflammatory genes (*Tnf-a*, *Il-6*, *Tlr-4*, and *Lbp*) showed a reciprocal increment in the said group. Melatonin co-treatment accounted for an improved status of antioxidant and anti-inflammatory genes as evidenced by their mRNA levels. High-fat high-fructose diet (HFFD) fed C57BL/6J mice recorded higher serum AST and ALT levels and fatty manifestation in histology of liver along with lowered mRNA levels of antioxidant (*Nrf2*, *Catalase*, and *Gss*) genes and Hgf. These set of parameters showed a significant improvement in HFFD + Mel.MSC group.

Conclusion: A significant improvement in viability of MSCs was recorded due to lowered intracellular oxidative stress and improves mitochondrial membrane potential. Further, melatonin-primed MSCs accounted for a significant decrement in fatty manifestations in liver and an improved physiological status of NAFLD in HFFD fed C57BL/6J mice. Taken together, it is hypothesized that melatonin priming to MSCs prior to its use can significantly augment the success of stem cell therapy.

Keywords: Melatonin, Non-alcoholic fatty liver disease, Stem cell therapy, Adipose-derived mesenchymal stem cells, NAFLD

Background

The ability of mammalian liver to undergo reparative regeneration in condition of hepatotoxic manifestations by a single or multiple factors is well established. Non-alcoholic fatty liver disease (NAFLD) is characterized by

*Correspondence: rv.devkar-zoo@msubaroda.ac.in
[1] Division of Metabolic Physiology and Endocrinology, Department of Zoology, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat 390002, India
Full list of author information is available at the end of the article

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Research Paper

Carbon monoxide releasing molecule-A1 improves nonalcoholic steatohepatitis via Nrf2 activation mediated improvement in oxidative stress and mitochondrial function

Kapil K. Upadhyay[a], Ravirajsinh N. Jadeja[b], Hitarthi S. Vyas[a], Bhaumik Pandya[c], Apeksha Joshi[a], Aliasgar Vohra[a], Menaka C. Thounaojam[d], Pamela M. Martin[b], Manuela Bartoli[d,**], Ranjitsinh V. Devkar[a,*]

[a] Metabolic Endocrinology Division, Department of Zoology, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, 390002, India
[b] Department of Biochemistry and Molecular Biology, Augusta University, Augusta, GA, 30912, USA
[c] Georgia Cancer Center, Augusta University, Augusta, GA, 30912, USA
[d] Department of Ophthalmology, Medical College of Georgia, Augusta University, Augusta, GA, 30912, USA

ARTICLE INFO

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ABSTRACT

Nuclear factor-erythroid 2 related factor 2 (Nrf2)-mediated signaling plays a central role in maintaining cellular redox homeostasis of hepatic cells. Carbon monoxide releasing molecule-A1 (CORM-A1) has been reported to stimulate up-regulation and nuclear translocation of Nrf2 in hepatocytes. However, the role of CORM-A1 in improving lipid metabolism, antioxidant signaling and mitochondrial functions in nonalcoholic steatohepatitis (NASH) is unknown. In this study, we report that CORM-A1 prevents hepatic steatosis in high fat high fructose (HFHF) diet fed C57BL/6J mice, used as model of NASH. The beneficial effects of CORM-A1 in HFHF fed mice was associated with improved lipid homeostasis, Nrf2 activation, upregulation of antioxidant responsive (ARE) genes and increased ATP production. As, mitochondria are intracellular source of reactive oxygen species (ROS) and important sites of lipid metabolism, we further investigated the mechanisms of action of CORM-A1-mediated improvement in mitochondrial function in palmitic acid (PA) treated HepG2 cells. Cellular oxidative stress and cell viability were found to be improved in PA + CORM-A1 treated cells via Nrf2 translocation and activation of cytoprotective genes. Furthermore, in PA treated cells, CORM-A1 improved mitochondrial oxidative stress, membrane potential and rescued mitochondrial biogenesis thru upregulation of Drp1, TFAM, PGC-1α and NRF-1 genes. CORM-A1 treatment improved cellular status by lowering glycolytic respiration and maximizing OCR. Improvement in mitochondrial respiration and increment in ATP production in PA + CORM-A1 treated cells further corroborate our findings. In summary, our data demonstrate for the first time that CORM-A1 ameliorates tissue damage in steatotic liver via Nrf2 activation and improved mitochondrial function, thus, suggesting the anti-NASH potential of CORM-A1.

1. Introduction

Multitude of metabolic diseases, including non-alcoholic steatohepatitis (NASH), have been implicated to higher consumption of fat-rich and high calorie foods [1]. About 15% of the total obese individuals with symptoms of metabolic syndrome constitute the high-risk group for NASH. Ethnicity, dietary habits, genetic and environmental factors further contribute towards the observed variations in occurrence of NASH [2,3]. Excess lipid accumulation in hepatocytes, high oxidative stress and inflammation are the key players in pathogenesis of NASH [4]. Currently used symptomatic treatment protocols for NASH include the lipid lowering, anti-diabetic, antioxidants or anti-inflammatory drugs coupled with changes in lifestyle. However, no FDA approved drug is presently available for this potentially lethal disease [5]. Patients with NASH develop anomalies in the ultrastructure of mitochondria, impairment of hepatic ATP synthesis and increased mitochondrial ROS production [6,7]. Lipid peroxidation, cytokine production and fatty manifestations in liver causes cell death and overall impairment of liver function [8].

The transcription factor nuclear factor erythroid 2-related factor 2

* Corresponding author.
** Corresponding author.
E-mail addresses: mbartoli@augusta.edu (M. Bartoli), rv.devkar-zoo@msubaroda.ac.in (R.V. Devkar).

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