Chhabra et al. (2017) Can J Biotech, Volume 1, Special Issue, Page 103
https://doi.org/10.24870/cjb.2017-a89

Canadian Journal of Biotechnology

ISSN 2560-8304

Poster Presentation **OPEN ACCESS**

Category: Functional Genomics

Hydrogen sulfide modulates basal metabolic circuitry − A transcriptome sequencing assisted insight

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Abstract

Hydrogen Sulfide (H_2S), the third gasomessenger to be discovered after nitric oxide (NO) and carbon monoxide (CO), is known for its distinctive health promoting effects on various organ systems, including cardiovascular system. This molecule has now qualified as an authentic mediator of specific cellular signal transduction pathways [1, 2]. The mechanistic insight into its cyto-protective role however remains incompletely understood. To understand the molecular circuitry regulated by H_2S augmentation, we utilized an exogenous donor of H_2S, Sodium hydrogen sulfide (NaHS), and performed unbiased global transcriptome sequencing (Illumina) in cardiac cells (H9c2 cardiomyoblasts). These experiments yielded differential transcriptome of the cells with varying levels of H_2S (with or without NaHS treatment for 6 hrs). We subjected this dataset to multiple pathway mining tools, including gene ontology analysis, functional annotation clustering and co-expression network analysis, to infer biological themes hidden as concerted differential gene expression signatures [3]. We, interestingly, observed common biological processes in different analysis strategies, suggesting authentic, conserved nature of cellular response to H_2S. Biological networks, largely associated with metabolic/ redox processes were recognized; within three gross themes− steroid/ isoprenoid biosynthesis, oxidoreductase coenzyme metabolism (representing pentose phosphate pathway, PPP) and glutathione metabolism. Glucose-6-phosphate dehydrogenase (G6PD)− rate-limiting enzyme within PPP stood as the highest degree node in majority of these networks. Also, genes related to oxidative stress and redox signaling were enriched. Interestingly, these pathways appear to be centrally linked by nicotinamide nucleotide cofactor (NADPH) homeostasis. We further supported this proposition at functional level by performing various enzyme activities besides recording cellular NADP/NADPH and GSH levels in established cellular as well as rat model system. In summary, our data suggested profound influence of H_2S on integrated cellular metabolic circuitry modulating redox homeostasis in cardiac cells.

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Citation: Chhabra, A., Bhargava, K. and Sharma, M. Hydrogen sulfide modulates basal metabolic circuitry − A transcriptome sequencing assisted insight [Abstract]. In: Abstracts of the NGBT conference; Oct 02-04, 2017; Bhubaneswar, Odisha, India: Can J biotech, Volume 1, Special Issue, Page 103. https://doi.org/10.24870/cjb.2017-a89

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