Gene 494 (2012) 130–139

Contents lists available at SciVerse ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Short Communication

Bio-informatics based analysis of genes implicated in alcohol mediated liver injury

Lakshmanan Jagannathan, Kavitha Swaminathan [1], S Mathan Kumar [1], G Ramesh Kumar, Aparajita Dey *

Life Science Division, AU-KBC Research Centre, MIT Campus of Anna University, Chromepet, Chennai-600044, India

ARTICLE INFO

Article history:
Accepted 15 November 2011
Available online 25 November 2011

Received by A.J. van Wijnen

Keywords:
Alcoholism
Hepatic dysfunction
Gene expression

ABSTRACT

Alcohol induced liver injury has been studied extensively. Using literature search and bioinformatics tools, the present study characterizes the genes involved in alcohol induced liver injury. The cellular and metabolic processes in which genes involved in alcohol induced liver injury are implicated are also discussed. The genes related to alcohol induced liver injury are also involved in affecting certain molecular functions and metabolism of drugs, besides being associated with diseases. In conclusion, the changes in regulation of genes implicated in alcohol induced liver injury apart from causing alcohol mediated hepatic dysfunction may affect other vital processes in the body.

1. Introduction

Alcohol induced liver injury is a well documented pathophysiological condition (Aziz-Seible et al., 2011; Lu and Cederbaum, 2008; Nath et al., 2011). Alcohol mediated induction of fatty liver may lead to subsequent development of hepatitis and cirrhosis (Bird and Williams, 1988; Seth et al., 2011). Several mechanisms through which alcohol predisposes liver to injury include increased oxidative stress, increase in pro-inflammatory cytokines, activation of anti-survival pathways and downregulation of anti-inflammatory and pro-survival genes (Aroor et al., 2010; Mandal et al., 2010; Miller et al., 2011; Pang et al., 2009; Seth et al., 2011; Wu and Cederbaum, 2009).

Alcohol mediated liver injury may involve changes in regulation of specific genes or gene transcripts i.e. certain genes which are detrimental for the normal structure and function of liver are upregulated and genes required for proper functioning of liver cells are down regulated (Anstee et al., 2011; Mandrekar, 2011). In a few instances, the 'good' genes are upregulated as protective machinery for the cell to survive against the alcohol insult. However, the overall picture is that of 'bad' genes being the key mediators of the harmful effects of alcohol and the 'good' genes are unable to mitigate the alcohol initiated downhill process of cell injury and death. The present study uses a bio-informatics based approach to characterize the various aspects of genes involved in alcohol mediated liver injury.

Abbreviations: (ATF4), Activating transcription factor 4; (ACOX), Acyl-CoA oxidase; (ADIPOR), Adiponectin; (ADH), Alcohol dehydrogenase; (ALDH), Aldehyde dehydrogenase; (ALAS1), 5-Aminolevulinic acid synthase-1; (ANXA2), Annexin A2; (APOB), Apolipoprotein B; (APOE), Apolipoprotein E; (ASNS), Asparagine. synthetase; (Acly), ATP-citrate lyase; (CPT1), Carnitine palmitoyl-CoA transferase I; (CASP 12), Caspase 12; (CAT), Catalase; (CHAC1/MGC4504), Cation transport regulator-like protein 1; (CTSL), Cathepsin L; (CHOP), C/EBP-homologous protein gene; (COL1A2), Collagen alpha2(I); (CYP2E1), Cytochrome P4502E1; (CYP 4A), Cytochrome P450 4A; (CS), Cytosolic sialidase; (COX-2), Cycloxygenase 2; (ET-1), Endothelin-1; (EPHX), Epoxide hydrolase; (L-FABP/FATP-2), Fatty acid binding protein; (Fasn), Fatty acid synthase; (2,3-ST), Gal-beta-1,3GlcNAc alpha 2,3-ST; (2,6-ST), Gal beta l, 4GlcNAc alpha2,6-sialyltransferase; (G6PD), Glucose 6 phosphatase; (GCK), Glucokinase; (GRP78), Glucose-regulated protein-78; (GCLC), Glutamate cysteine ligase catalytic subunit; (GSTM1), Glutathione-S-transferases M1; (GADD34/PPP1R15A), Growth arrest and DNA damage-inducible protein; (GADD153/DDIT3), Growth arrest and DNA damage-inducible gene 153; (GAPDH), Glyceraldehyde-3-phosphate dehydrogenase; (Hsp70 / hsc73), 73 kDa heat shock cognate; (HO-1), Heme oxygenase; (HIF-1alpha), Hypoxia-inducible factor-1alpha; (iNOS), Inducible NO synthase; (IGFBP-1/ PP12), Insulin-like growth factor-binding protein 1 / placental protein 12; (IGF-1), Insulin like Growth factor-1; (IL), Interleukin; (ISR), Integrated stress response; (LCAD), Long chain acyl-CoA dehydrogenase; (Mod1), Malic enzyme; (MMPs), Matrix metallo-proteinases; (MCAD), Medium-chain acyl-CoA dehydrogenase; (MAT), Methionine adenosyl Transferase; (MT), Metallothionein; (MTP), Microsomal triglyceride transfer protein; (MPO), Myeloperoxidase; (POR), NADPH Cytochrome P450 Oxidoreductase; (NQO1), NADPH quinone oxidoreductase; (NF-kappaB), Nuclear Factor-kappa B; (Nrf2), NF-E2-related factor 2; (PPAR alpha), Peroxisome proliferators-activated receptor alpha; (FACO), Peroxisomal fatty acyl CoA oxidase; (PTEN), Phosphatase and tensin homolog deleted on chromosome ten; (PMS), Plasma membrane sialidase; (PLG), Plasminogen; (PAI-1/SERPINE1), Plasminogen activator inhibitor-1; (PGC-1alpha), PPAR-gamma coactivator 1 alpha; (PCNA), Proliferating cell nuclear antigen; (PKC), Protein Kinase C; (RXRalpha), Retinoid X receptor alpha; (ST), Sialyltransferase; (STAT3), Signal transducer and activator of transcription 3; (SIRT1), Sirtuin 1; (Scd1), Stearyl-CoA desaturase; (SRE), Sterol regulatory element; (Srebf1), binding factor 1; (SREBP1), SRE-binding protein 1; (SREBP-1c), Sterol response element binding protein-1c; (SOD), Superoxide dismutase; (TLR3), Toll-like receptor 3; (TNF-alpha), Tumor necrosis factor alpha; (TIMP), Tissue inhibitors of matrix metallo-proteinases; (TRB3), Tribbles 3; (XBP-1), X-box binding protein- 1.

* Corresponding author at: AU-KBC Research Centre, MIT Campus of Anna University, Chromepet, Chennai-600044, India. Tel.: +91 44 2223 4885x149, 91 9790848299; fax: +91 44 2223 1034.
E-mail addresses: aparajitabhu@rediffmail.com, aparajitadey21@gmail.com (A. Dey).
[1] Both authors have made equal contributions.

0378-1119/$ – see front matter
doi:10.1016/j.gene.2011.11.031

2. Methods

Pubmed search for the terms 'alcohol, liver, genes' yielded 1323 results. We selected 75 references involving almost 85 genes. Since a large number of studies in literature have documented alcohol mediated liver injury, the study has been limited to certain specific alcohol regulated genes which have been extensively studied in this context or have very profound implications on the occurrence of alcohol induced liver injury.

The human homologues of the genes expressed in the rodent animals were selected from the database of Human Gene Nomenclature Committee. Further, the ToppFun bioinformatics tool was used to study the various parameters. Sixteen diseases in which alcohol regulated hepatic genes were observed and all of them were significant. The database search yielded 1206 drugs which are metabolized by alcohol responsive genes in liver, 586 drugs were significant and 83 drugs have been represented. A list of 569 metabolic processes catalyzed by alcohol responsive genes in liver was observed, of which 314 were significant and 50 metabolic processes are represented. Alcohol regulated genes in liver were found to exhibit 48 molecular functions but 9 were insignificant. Alcohol regulated hepatic genes were found to metabolize 30 biological pathways, of which 21 were significant. Bonferroni's method was used to analyze the significance of the bioinformatics data and $p<0.05$ was considered to be significant.

3. Results

3.1. Pubmed search

The alcohol regulated hepatic genes or gene products i.e. proteins selected from Pubmed references with their specific actions and changes in regulation due to alcohol exposure are listed in Table 1 and Supplementary Table S1. The hepatic genes or gene products i.e. proteins with changes in regulation due to alcohol exposure can be broadly classified into following groups: genes/proteins implicated in alcohol metabolism; genes/proteins involved in oligosaccharide synthesis and degradation; stress response genes/proteins; genes/proteins involved in fatty acid metabolism; genes/proteins involved in glucose metabolism; genes involved in heme synthesis and degradation; genes involved in fibrin synthesis and degradation; genes involved in lipid metabolism; anti-apoptotic genes/proteins; genes involved in cancer progression and development; genes encoding antioxidants; genes involved in inflammation; calcium responsive genes; genes involved in cellular growth; genes encoding for Interleukins; genes/proteins involved in immune responses; genes involved in extracellular matrix degradation; genes involved in methionine metabolism; genes involved in signal transduction; genes involved in energy metabolism; genes involved in protein metabolism and genes/proteins involved in DNA repair. The results of gene ontology analysis of genes implicated in alcohol induced liver injury are diagrammatically represented in Fig. 1.

3.2. Disease analysis

Genes mediating alcohol induced liver injury showed varied association with other diseases (Table 2 and Supplementary Table S2). Genes implicated in alcohol induced liver injury showed maximal association (≥80%) with pathophysiological conditions such as osteoporosis; oral submucosal fibrosis; squamous cell carcinoma, and fever. Genes implicated in alcohol mediated liver injury showed ≥ 60% but <80% association with diseases such as breast, stomach, urinary bladder and prostrate neoplasms, experimental liver cirrhosis, and sepsis.

Diseases in which genes implicated in alcohol induced liver injury showed moderate association (≥50% but <60%) include pulmonary fibrosis, lung neoplasms, and multiple myeloma, and least association (<50%) was observed in sciatic neuropathy.

3.3. Drug metabolism

Among the list of selective drugs that are metabolized by genes implicated in alcohol induced liver injury, most of them could be broadly classified into anti-inflammatory, antibiotics, or anti- cancer drugs (Table 3 and Supplementary Table S3). The drugs which are metabolized by ≥80% of alcohol related hepatic genes among the total list of the genes involved in the metabolism of the specific drug, include the wide spectrum antibiotics erythromycin estolate and puromycin, drug used for treatment of chronic alcoholism-disulfiram, anti-inflammatory drugs sulfasalazine, 5-aminosalicylic acid and luteolin, anti-bacterial drugs tetracycline and cephaloridine; antidote for methanol or ethylene glycol poisoning fomepizole, neuroprotective agent edaravone, cholesterol lowering agent ezetimibe, anti-diabetic drug rosiglitazone, anti-cancer drugs ursolic acid, 17-N- Allylamino-17-demethoxygeldanamycin and cyclophosphamide, anti-fungal and anti-hypertensive drug staurosporine, analgesic and antipyretic drug acetaminophen, lipid lowering drug bezafibrate, anti-tuberculosis drug isoniazid, antihypertensive drug amlodipine and psychostimulant amphetamine.

The list of drugs metabolized by ≥60% but <80% alcohol specific hepatic genes among total genes specific for each drug include the drug used for treatment of myelodysplastic syndrome decitabine, anticancer drugs farnesol, docetaxel, bexarotene and bleomycin, antiretroviral ritonavir, drug for treating multiple myeloma- bortezomib, drug for treatment of hypertension and congestive heart failure- amiloride, anti-diabetic pioglitazone, drug for intermittent claudication- pentoxifylline, anti-rheumatic agent auranofin, anti-inflammatory agents berberine and 5-aminosalicylic acid, the immunosuppressant neoral, lipid lowering agent simvastatin, cholesterol lowering agent rosuvastatin, drug used for treatment of progeria ionofarnib, antithyroid drug methimazole, and antimalarial drug chloroquine.

The drugs which are metabolized by ≥50% but <60% of alcohol related hepatic genes among the total list of the genes involved in the metabolism of the specific drug, include antifungal antibiotic trichostatin A, opiate analgesic morphine, phosphodiesterase inhibitor dibutyryl cyclic AMP, drug for hypertension and congestive heart failure quinapril, anti-inflammatory drug naproxen and anti-hypertensive drugs valsartan and irbesartan.

3.4. Metabolic processes

Table 4 and Supplementary Table S4 show the list of genes implicated in alcohol mediated liver injury which are also involved in metabolic pathways. The metabolic pathways in which ≥80% of alcohol related hepatic genes among the total list of the genes involved are implicated include regulation of ketone metabolism, positive regulation of catabolism, chemokine production and its regulation and ER-nucleus signaling pathway.

The metabolic pathways in which ≥60% but <80% of alcohol related hepatic genes among the total list of the genes involved are implicated include cellular carbohydrate metabolism, positive regulation of protein and RNA metabolism, protein oligomerization, fat cell differentiation, regulation of DNA binding, transcription from RNA polymerase II promoter and its regulation, lipid, fatty acid and monocarboxylic acid catabolism, DNA-dependent positive regulation of transcription, regulation of fatty acid metabolism, drug response reactions, positive regulation of developmental processes or cytokine