Vinyl carbamate activates the alternative complement pathway in glomerular endothelial cells and induces membranoproliferative glomerulonephritis

Athena Gong[1], Deepak Malhotra[2], William T. Gunning[3], Lance Dworkin[4], Mengxuan Chen[5*]

[1]University of Michigan Medical School, 1301 Catherine Street, University of MIchigan, Ann Arbor MI 48109

[2]Professor and Endowed Professor of Medicine, Division of Nephrology, Department of Medicine, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

[3]Professor, Director of Electron Microscopy, Department of Pathology, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

[4]Professor and Mercy Health Endowed Chair in Education, Division of Nephrology, Department of Medicine, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

[5]Research Assistant, Division of Nephrology, Department of Medicine, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

Email: mengxuan.chen@utoledo.edu

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Background: Vinyl carbamate (VC) is a carcinogenic metabolite of ethyl carbamate (EC), which is a process contaminant in fermented foods and alcoholic beverages. While EC and VC are recognized for their tumorigenic effects, their impact on the kidney has not been previously studied.

Methods: A/J inbred mice received a single i.p. injection of VC (60 mg/kg). Kidney injury was evaluated. A post hoc analysis was performed on a publicly available RNA-Seq transcriptome of kidneys from rats treated with fermented wine containing high levels of EC.

Results: Beginning 5 weeks post VC injection, mice showed signs of moribund state and were killed. By 12 weeks, a total of 97 of the 240 treated mice had died or were killed. Necropsies revealed evident renal disease, characterized by glomerular lobularization, mesangial hypercellularity and expansion, endocapillary proliferation, and capillary wall thickening by light microscopy. Electron microscopy

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showed subendothelial deposits, new basement membrane formation, and extensive podocyte foot process effacement. Immunofluorescence indicated abundant granular C3 staining in the mesangium and coarse linear capillary staining, resembling membranoproliferative glomerulonephritis (MPGN). Additionally, Kyoto Encyclopedia of Genes and Genomes pathway enrichment analyses were performed on differentially expressed genes between high EC-treated and control rats, and showed that complement and coagulation cascades are top predicted biological processes implicated. Furthermore, pathway-based data integration and visualization using Pathview demonstrated that key regulators of complement activation pathways were altered by high EC treatment. Notably, complement factor (CF) D and H, critical positive and negative regulators of the alternative pathway, respectively, were the most affected, with CFD induced by 3.49-fold and CFH repressed by 5.88-fold, underscoring a hyperactive alternative pathway.

Conclusion: VC, a metabolite of EC, induces complement fixation in glomeruli and MPGN in mice. Complement overactivation due to CFD induction and CFH repression may be an underlying pathomechanism.

Keywords: Complement, C3 Glomerulonephritis, C3 Glomerulopathy, Glomerular Endothelial Cells, Dense Deposit Disease

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