BURN INJURY, ALCOHOL, AND GUT ORGANOID GENE EXPRESSION

ABSTRACT

Burn injuries remain a major source of morbidity and mortality worldwide and present clinicians with a complex set of challenges related to wound management, systemic inflammation, and multi-organ dysfunction. A striking epidemiologic feature of burn trauma is the high frequency with which alcohol intoxication co-occurs at the time of injury. Nearly half of burn patients in the United States present with measurable blood alcohol concentrations, and numerous studies have demonstrated significantly worse outcomes in this population [1,2]. Despite consistent clinical associations, the mechanisms linking alcohol intoxication to worsened burn outcomes remain incompletely understood.

Growing attention has been directed toward the gastrointestinal tract as a key driver of post-burn morbidity. The intestinal epithelium forms a dynamic barrier that protects against microbial translocation and contributes to systemic immune homeostasis. Burn injury disrupts this barrier through epithelial apoptosis, breakdown of tight junctions, impaired epithelial regeneration, and altered innate immune signaling [3,4]. Alcohol independently compromises the intestinal barrier by altering the mucus layer, increasing permeability, impairing antimicrobial peptide production, and promoting intestinal dysbiosis [5,6]. When burn injury and alcohol exposure occur together, the resulting impairment in intestinal defense is often greater than either insult alone [7,8].

Interleukin-22 (IL-22) is a cytokine crucial for coordinating epithelial regeneration and antimicrobial defense. IL-22 induces antimicrobial peptides such as Regenerating islet-derived protein 3 gamma (Reg3γ) and membrane-bound mucins such as Mucin-1 (Muc1), both essential for maintaining intestinal barrier integrity [9–13]. Reg3γ is a C-type lectin that restricts microbial proximity to the epithelial surface, while Muc1 contributes to epithelial protection through anti-adhesive and immune-modulatory functions.

This study used a murine burn model paired with ex vivo colonic organoid cultures to investigate how ethanol exposure affects IL-22-mediated expression of Reg3γ and Muc1 following burn injury. Organoids were cultured from colonic crypts isolated from sham-injured and burn-injured mice, exposed to ethanol or vehicle, stimulated with IL-22, and analyzed using quantitative RT-PCR.

IL-22 robustly induced Reg3γ and Muc1 expression under all conditions. Ethanol significantly suppressed IL-22-induced Reg3γ expression in organoids derived from burn-injured mice, producing a 68 percent reduction compared with IL-22 stimulation alone. This effect was not observed in sham-derived organoids. Muc1 expression remained IL-22-dependent and unaffected by burn injury or ethanol exposure. These findings highlight selective vulnerability within IL-22-responsive antimicrobial pathways following combined burn injury and ethanol exposure.

Understanding how trauma and alcohol reshape epithelial antimicrobial responses is essential for designing interventions to reduce infection risk and systemic inflammation in intoxicated burn patients. This study demonstrates that combined burn injury and ethanol exposure impair IL-22-mediated Reg3γ expression but preserve Muc1 induction, revealing divergent responses among epithelial defense pathways and shedding light on mechanisms underlying increased susceptibility to complications in intoxicated burn patients.

REFERENCES

1. Silver GM, Albright JM, Schermer CR, et al. Adverse clinical outcomes associated with elevated blood alcohol levels at the time of burn injury. *J Burn Care Res.* 2008;29:784–789.

2. Davis CS, Esposito TJ, Palladino-Davis AG, et al. Implications of alcohol intoxication at the time of burn and smoke inhalation injury. *J Burn Care Res.* 2013;34(1):120–126.

3. Huáng Z, Huáng Y, Chen J, et al. The role and therapeutic potential of gut microbiome in severe burn. *Front Cell Infect Microbiol.* 2022;12:974259.

4. Corcione S, Lupia T, De Rosa FG; Host and Microbiota Interaction Study Group (ESGHAMI) of ESCMID. Microbiome in the setting of burn patients: implications for infections and clinical outcomes. *Burns Trauma.* 2020;8:tkaa033.

5. Yue R, Wei X, Zhao J, et al. Essential role of IFN-γ in regulating gut antimicrobial peptides and microbiota to protect against alcohol-induced bacterial translocation. *Front Physiol.* 2021;11:629141.

6. Slomiany A, Piotrowski E, Piotrowski J, et al. Impact of ethanol on innate protection of gastric mucosal epithelial surfaces and the risk of injury. *J Physiol Pharmacol.* 2000;51(3):433–447.

7. Mendes BG, Schnabl B. From intestinal dysbiosis to alcohol-associated liver disease. *Clin Mol Hepatol.* 2020;26(4):595–605.

8. Li X, Hammer AM, Rendon JL, Choudhry MA. Intestine immune homeostasis after alcohol and burn injury. *Shock.* 2015;43(6):540–548.

9. Mizoguchi A. Healing of intestinal inflammation by IL-22. *Inflamm Bowel Dis.* 2012;18(9):1777–1784.

10. Kolls JK, McCray PB Jr, Chan YR. Cytokine-mediated regulation of antimicrobial proteins. *Nat Rev Immunol.* 2008;8(11):829–835.

11. Parks OB, Pociask D, Hodzic Z, et al. Interleukin-22 signaling in the regulation of intestinal health and disease. *Front Cell Dev Biol.* 2016;3:85.

12. Sheng Y, Triyana SY, Wang R, et al. MUC1 and MUC13 differentially regulate epithelial inflammation in response to inflammatory and infectious stimuli. *Mucosal Immunol.* 2013;6(3):557–568.

13. Paone P, Cani PD. Mucus barrier, mucins and gut microbiota: the expected slimy partners? *Gut.* 2020;69(12):2232–2243.

14. Wang L, Fouts DE, Stärkel P, et al. Intestinal REG3 lectins protect against alcoholic steatohepatitis. *Cell Host Microbe.* 2016;19(2):227–239.

15. Wheatley EG, Curtis BJ, Hulsebus HJ, et al. Advanced age impairs intestinal antimicrobial peptide response and worsens dysbiosis following burn injury in mice. *Shock.* 2020;53(1):71–77.

16. Shin JH, Seeley RJ. Reg3 proteins as gut hormones? *Endocrinology.* 2019;160(6):1506–1514.

17. Shin JH, Bozadjieva-Kramer N, Shao Y, et al. Reg3g links microbiome to energy balance. *Cell Metab.* 2022;34(11):1765–1778.

18. Xiao Y, Huang X, Zhao Y, et al. IL-33 promotes REG3γ expression and regulates gut microbiota. *Cell Mol Gastroenterol Hepatol.* 2019;8(1):21–36.

19. Sundnes O, Ottestad W, Schjalm C, et al. Rapid systemic surge of IL-33 after severe trauma. *Mol Med.* 2021;27(1):21.

20. Hodzic Z, Schill EM, Bolock AM, et al. IL-33 and the intestine: the good, the bad, and the inflammatory. *Cytokine.* 2017;100:1–10.