Smoking and Drinking Synergize in Pancreatitis: Multiple Hits on Multiple Targets

See "The Combination of alcohol and cigarette smoke induces endoplasmic reticulum stress and cell death in pancreatic acinar cells," by Lugea A, Gerloff A, Su H-Y, et al, on page 1674.

Acute pancreatitis is the first stage of an inflammatory disease continuum in the pancreas that can progress through recurrent acute pancreatitis to chronic pancreatitis, and which is driven by genetic susceptibility and environmental risk factors. Although many of these individual factors have been identified and investigated as potential targets for therapy, there is still no specific intervention to prevent or treat disease onset and progression. One of the likely reasons for therapeutic failure is that the pathogenesis of pancreatitis involves.

"multiple hits on multiple targets" (Figure 1) and we have an insufficient understanding regarding the synergism among the various risk factors that can amplify harmful effects. In this issue of *Gastroenterology*, Lugea et al[1] shed new light on this problem by identifying a pathologic pathway through which smoking and alcohol interact and worsen acinar cell injury and pancreatitis.

The longest studied environmental risk for acute pancreatitis is alcohol abuse, which affects both disease onset and progression by multiple mechanisms. Mechanistically, alcohol exerts its deleterious effect on multiple targets, altering the function of pancreatic acinar, ductal, and stellate cells alike.[2–11] At the cellular level, alcohol (i) induces mitochondrial damage, (ii) elevates intracellular calcium levels, (iii) disrupts expression and function of the cystic fibrosis transmembrane conductance regulator (CFTR), (iv) decreases bicarbonate secretion, (v) increases pancreatic digestive enzyme content, (vi) redirects exocytosis to the basolateral surface, (vii) enhances pancreatitis responses elicited by hyperstimulation, (viii) induces endoplasmic reticulum (ER) stress, (ix) promotes oxidative stress, (x) increases the fragility of lysosomes and zymogen granules, and (xi) activates stellate cells to promote fibrosis. Genetic susceptibility can potentiate the effects of alcohol and variants at the *CLDN2-MORC4, CTRB1-CTRB2, CTRC, PRSS1-PRSS2,* and *SPINK1* loci have been conclusively associated with alcohol-related pancreatitis.[12] Notably, many of these genetic variants have relatively small effects on their own, and the combination of multiple genetic variants and alcohol is required for pancreatitis onset. In mouse experiments, genetic deletion of *Cftr* resulted in more intense pancreatitis responses elicited by alcohol and fatty acid injections.[4] Despite the multitude of targets affected, alcohol alone does not induce acute or chronic pancreatitis in animal models unless additional pathogenic insults are present, such as administration of fatty acids, lipopolysaccharides, secretagogue hyperstimulation or viral infection.[2,13] It is remarkable, how alcohol can synergize with a number of seemingly unrelated disease-causing agents to produce a common pathologic outcome, namely, pancreatitis.

More recent epidemiologic studies have revealed that smoking is an equally widespread risk factor for

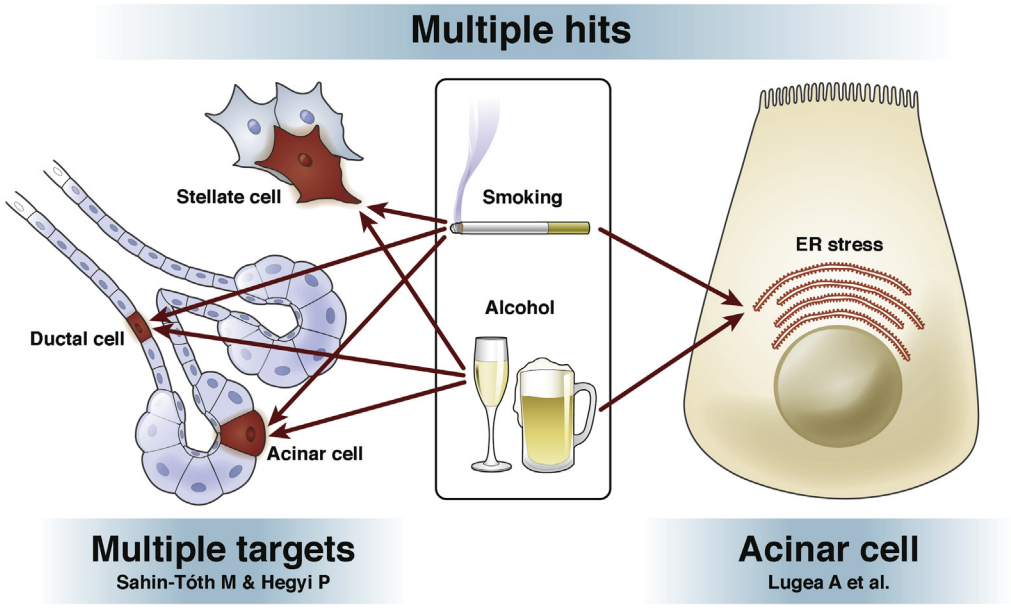

Figure 1. The "multiple hits on multiple targets" model of pancreatitis pathogenesis associated with cigarette smoking and alcohol abuse. Lugea et al identified acinar cell endoplasmic reticulum (ER) stress as a novel mechanism of synergy between alcohol and smoking.

pancreatitis.[14] Smoking is associated with earlier onset of chronic disease and the appearance of calcifications and diabetes, independent of alcohol consumption. Similar to alcohol, cigarette smoke also affects pancreatic acinar, ductal, and stellate cells with similar perturbations in function.[15–17] Thus, smoking (i) induces oxidative stress, (ii) inhibits CFTR, (iii) decreases fluid and bicarbonate secretion, and (iv) stimulates pancreatic fibrosis. Smoking often goes hand-in-hand with alcoholism, and together their deleterious effects can amplify the risk for pancreatitis. However, it has been unclear whether smoking and alcohol act simply by an additive effect of otherwise independent risk factors or by synergizing via so far unknown mechanisms.

The unfolded protein response (UPR) is an adaptive cellular signaling event triggered by ER stress owing to the accumulation of unfolded and/or misfolded proteins in the ER. Unresolved ER stress can lead to maladaptive responses with up-regulation of the proapoptotic transcription factor *CCAAT-enhancer-binding protein homologous protein* (CHOP, also known as *DNA damage-inducible transcript 3* [DDIT3]) and consequent cell death. In a previous study, the authors demonstrated that alcohol up-regulates the *Inositol-requiring enzyme 1* (IRE1) arm of the UPR, resulting in higher levels of the spliced form of the transcription factor *X-box binding protein 1* (XBP1), which protects against injurious activation of the *protein kinase RNA (PKR)-like ER kinase* (PERK) arm that is linked to CHOP up-regulation and apoptosis.[6] In the present study, Lugea et al[1] elegantly demonstrate using cellular and animal experiments that smoking down-regulates spliced XBP1 and thereby blocks the adaptive response to alcohol, and redirects it to a maladaptive response of CHOP up-regulation, cellular injury, and stronger pancreatitis responses.[1] Although the exact mechanism of XBP1 down-regulation by smoking remains unclear, the concept that smoking and other environmental and/or genetic factors can worsen ER stress by targeting the IRE1–XBP1 pathway may be generally applicable to a variety of pathologic situations. Finally, the experiments also suggest that therapeutic interventions that increase XBP1 levels should be protective against the synergistic effects of alcohol and smoking.

Activation of the UPR in acute and chronic pancreatitis has been observed previously.[18,19] Compelling evidence that ER stress may play a direct pathogenic role in pancreatitis came from human genetic studies and functional analysis of disease-associated mutations. Thus, mutations that induce misfolding of the most abundantly expressed digestive enzymes cationic trypsinogen (PRSS1) and carboxypeptidase A (CPA1) elicit ER stress in acinar cells and cause hereditary or sporadic chronic pancreatitis.[20] Interaction of smoking with genetic mutations has not yet been investigated but based on the new findings of Lugea et al,[1] one can assume that smoking would synergize with misfolding digestive enzyme mutants to cause acinar cell death by reducing protective XBP1 levels and promoting up-regulation of CHOP.

In summary, Lugea et al[1] now identify a novel mechanism of synergy between alcohol and cigarette smoke in causing unresolved ER stress and acinar cell death that, in turn, worsens pancreatitis responses. Based on prior studies, we can predict that ER stress and the associated UPR is just one example of many signaling pathways within the "multiple hits on multiple targets" model by which pancreatitis develops (Figure 1). The discovery of novel sites of synergy between genetic and environmental risk factors that drive pancreatic inflammation is an exciting future prospect in pancreatology.

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Conflicts of interest
The authors disclose no conflicts.

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