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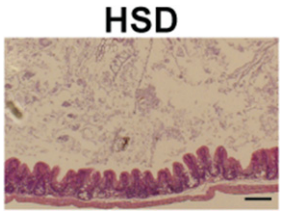
High Salt Diets Exacerbate IBD

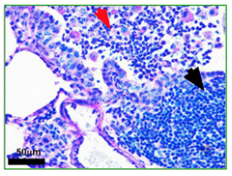


The Western Diet, which is characterized by high fat, protein, and sugar and low fiber intake, has been associated with diseases of the developed world such as atherosclerosis, diabetes, and inflammatory bowel disease (IBD). Given that salt is first encountered in the gastrointestinal tract, it is perhaps surprising that the effect of sodium chloride, a defining feature of processed foods, on IBD has not been investigated in depth despite numerous studies indicating that high salt diets (HSDs) are proinflammatory. In this issue, Tubbs et al. (p. 1051) investigated the effects of a HSD in murine models of colitis. Mice on a HSD, which had comparable sodium content to fast food, showed high concentrations of sodium in the feces, stomach, and colon when compared with mice fed a low salt diet (LSD). In the IL-10–deficient model of spontaneous colitis, mice on a HSD showed exacerbated inflammatory colitis pathology relative to mice fed a LSD, and this correlated with increased expression of genes encoding proinflammatory cytokines, including *Tnf, Il12b*, *Il23a*, and *Il1b*. Similar to the IL-10–deficient model, mice on a HSD infected with *Salmonella typhimurium* also had increased expression of proinflammatory cytokines by day 3 of infection, suggesting that a HSD may enhance innate immune responses. Consistent with this, LPS-stimulated dendritic cells (DCs) exposed to high salt media (HSM) produced significantly more pro–IL-1β, IL-12p40, and IL-23p19 than controls. This effect appeared to be dependent on signaling events downstream of TLR4 activation, as addition of either p38 or SGFK1 inhibitors to LPS-stimulated DCs in HSM reduced proinflammatory cytokine production when compared with untreated controls. Therefore, this study demonstrates that a HSD creates a high local concentration of sodium in the colon that exacerbates a murine model of chronic, immune-mediated colitis and indicates that a high level of dietary salt may be detrimental to individuals with IBD.

Teasing Apart *Tcrb* Transcription

Cooperative binding of the transcription factors RUNX1 and ETS1 to the Eβ enhancer in the *Tcrb* locus is important for the initiation of DβJβ gene recombination in double-negative thymocytes. To determine whether RUNX1 and ETS1 play independent roles during activation of the *Tcrb* locus, Zhao et al. (p. 1131) monitored recombination in a thymoma cell line in which one allele lacked the *Tcrb* recombination center (including both DβJβ clusters and Eβ). Replacement of the ETS or RUNX motifs in Eβ with binding sites for the yeast transcription factor Gal4 prevented ETS1 and RUNX1 binding to Eβ and impaired germline transcription at the *Tcrb* locus, confirming that the two ETS-RUNX composite motifs in Eβ are required for the enhancer's function in this cell line. Tethering of RUNX1 to these Gal4 Eβ mutants by replacing the Runt domain of RUNX1 with the Gal4 DNA-binding domain rescued Eβ function. Cooperative binding of ETS1 was not required for this rescue, as demonstrated by the restoration of Eβ function even after destruction of ETS binding motifs in Eβ, which prevented recruitment of ETS1 to Eβ. Experiments to tease apart the relative activity of RUNX1 functional domains suggested that Eβ activation required either strong binding of RUNX1 alone or the recruitment of ETS1 together with the presence of RUNX1, and the negative regulatory domain for DNA binding (NRDB) of RUNX1 was unexpectedly not necessary for ETS1 recruitment to Eβ. However, in the absence of NRDB, the transactivation domain (TAD) of RUNX1 could partially activate germline transcription of only the most proximal promoter in the *Tcrb* locus, suggesting that the NRDB was important for RUNX1 activity if not ETS1 binding. Intact RUNX1 alone could also mediate nucleosome clearance at *Tcrb* promoters and enhancer-promoter looping when tethered to Eβ via Gal4 binding. Taken together, these data suggest that ETS1 is important for cooperative binding with RUNX1 to Eβ but not for germline transcription of the *Tcrb locus*, and that, if efficiently recruited to Eβ, RUNX1 can function independently of ETS1 to activate the *Tcrb* locus.

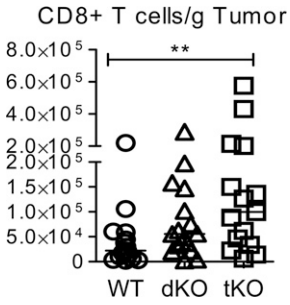
Early Secondhand Smoke Exposure Worsens Lung Disorders



Previous studies using *Scnn1b* transgenic (*Scnn1b*-Tg$^+$) mice, which model muco-obstructive airway diseases such as cystic fibrosis, have highlighted the negative effects of short term secondhand smoke (SHS) exposure on these diseases. However, the specific effects of SHS exposure on initiation and progression of muco-obstructive lung diseases remain unclear. In this issue, Lewis et al. (p. 1170) began exposing *Scnn1b*-Tg$^+$ mice to SHS (SHS-Tg$^+$) on postnatal day (PND) 3 and showed that when compared with *Scnn1b*-Tg$^+$ mice exposed to filtered air (FA-Tg$^+$), SHS exposure suppressed recruitment of neutrophils, eosinophils, and lymphocytes to the airspaces at PND22. This was likely due to significant reductions of MCP-1, eotaxin, and IL-5 observed in the bronchoalveolar lavage fluid (BALF) of SHS-Tg$^+$ mice when compared with FA-Tg$^+$ controls. Additionally, SHS-Tg$^+$ mice showed diminished IgA levels in the BALF and were unable to clear spontaneous bacterial infections, which FA-Tg$^+$ mice were able to resolve by PND22. SHS-Tg$^+$ mice also showed significant reductions in mucous cell metaplasia and mucus obstruction, which are pathological features of the *Scnn1b*-Tg$^+$ mouse model, and these changes were attributed to a reduced Th2 environment in the lungs as

indicated by decreased levels of IL-5, IL-4, and IL-13 in the BALF and a downregulation of Th2/mucous cell metaplasia-related genes. This suppression of Th2 responses in SHS-Tg$^+$ mice was associated with reduced production of IL-33, a known stimulator of type II innate lymphoid cells, by alveolar epithelial cells and alveolar macrophages. Finally, cessation of SHS exposure for 21 d restored suppressed responses, but SHS-Tg$^+$ mice continued to exhibit an exaggerated degree of airway inflammation, epithelial necrosis, parenchymal consolidation, and lymphoid hyperplasia when compared with FA-Tg$^+$ mice. Collectively, these data demonstrate that early exposure to SHS of individuals with muco-obstructive lung diseases may predispose them to lung bacterial infections due to reduced IL-33–dependent neutrophil recruitment and diminished Th2 responses. Although these effects may be reversed upon cessation of SHS exposure, SHS-exposed muco-obstructive lungs may exhibit exaggerated pathological alterations which can have long-term consequences in later life.

Reducing Immunotherapy-Associated Autoimmunity



Despite their clinical potential, widespread application of antitumor therapies such as CTLA-4 and PD-1 blockade has been hindered by potentially lethal off target autoimmune side effects. These antitumor therapies can block T regulatory cell (Treg) function, and previous studies demonstrated that blockade of OX40 and CD30 costimulatory signals abolished CD4$^+$ T cell-driven autoimmunity in Foxp3-deficient mice, suggesting that this double blockade could also be efficacious in the context of tumor therapy. In this issue, Nawaf et al. (p. 974) investigated whether ablation of OX40/CD30 signals could attenuate CD4$^+$ T cell–driven autoimmunity associated with anti–CTLA-4/anti–PD-1 immunotherapy while preserving antitumor immunity. When compared with wild-type (WT) or OX40/CD30-deficient tumor bearing controls, mice deficient in Foxp3, OX40, and CD30 (triple knockout mice [tKO]) demonstrated significantly reduced tumor growth following implantation of melanoma tumor cells, which correlated with increased CD8$^+$ and decreased CD4$^+$ tumor-infiltrating cells. Additionally, CD8$^+$ tumor-infiltrating cells in tKO mice showed significant upregulation of inhibitory receptors PD-1 and CTLA-4, and depletion of CD8$^+$ T cells in tKO mice led to rapid growth of tumors when compared with controls. Administration to tumor-bearing WT mice of blocking Abs to CTLA-4 and PD-1, either alone or in combination, slowed tumor growth but resulted in significant off target liver immunopathology when compared with control-Ab treated mice. Addition of OX40L or CD30L blocking Abs to CTLA-4/PD-1 blockade did not enhance the ability of CTLA-4/PD-1 blockade to control tumor growth but instead resulted in a higher proportion of CD8$^+$ than CD4$^+$ T cells infiltrating tumors and significantly reduced liver pathology. Therefore, this study demonstrates that blockade of OX40 and/or CD30 signals may be an effective way to reduce CD4$^+$ T cell–driven toxicity associated with CTLA-4 and PD-1 blockade for cancers in which CD8$^+$ T cells are the main effectors of the antitumor response, thereby potentially opening up this therapy to patients with less advanced diseases.