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Abstract:
Exposure to secondhand smoke (SHS) is associated with a greater lifetime risk of developing asthma, more severe asthma, and increased asthma hospitalizations for both children and adults. While much of the immunopathogenesis of asthma remains incompletely understood, key molecular events include changes in regulatory T cell (Treg) and effector T cell (Teff) activity in response to exposure to several air pollutants including SHS. Previous results from the Nadeau and Miller research groups suggest that Treg and Teff are epigenetically regulated, and their alterations affect the expression of several asthma genes and asthma- related clinical outcomes. While exposure to SHS has been shown to induce epigenetic alterations, and epigenetic changes in asthma genes may be associated with asthma, causal relationships have not been demonstrated. This proposal will try to establish a novel approach of SHS research by determining relationships between SHS exposure and asthma using uniquely linked mechanistic studies and an innovative study design. Key to this proposal is the intent to conduct studies in a well-phenotyped monozygotic twin (MZT) cohort including cases discordant on exposure to SHS and asthma that can determine the association of SHS-induced epigenetic marks, and the timing of this association, on asthma in the absence of differences in genetic backgrounds and in utero and early childhood environmental exposures, methodological limitations from prior studies. We hypothesize that exposure to SHS is associated with current asthma in adults, and this association is mediated through DNA methylation of asthma genes in Treg and Teff cells and the consequential downstream cellular events. Specifically, to understand the mechanisms of SHS-induced pathology in asthma and inflammation, we propose to: Aim 1: Test whether CpG methylation levels of specific genetic loci are altered in MZT discordant for smoking and asthma. Aim 2. Determine if minimization of exposure to SHS is associated with a decrease in methylation of Foxp3, IL-10, in Treg, and IFNg in Teff and an increase in methylation of IL-4 in Teff over time. Aim 3. Determine how methylation levels of Foxp3, IL-10, IFNg, IL-4 are influenced by never, prior (only *in utero* or only childhood), or current SHS exposure in asthmatic and nonasthmatic twins by estimating main effects and interactions and controlling for period of asthma onset. If the aims are achieved, this proposal should improve our understanding of the mechanisms by which exposure to SHS contributes to asthma and identify novel biomarker of smoke-related airway disease so that environmental policy and risk management can be developed more effectively, and screening and/or therapeutic interventions may be instituted earlier.