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Genetic, laboratory and clinical factors associated with low-dose aspirin failure in the prevention of preeclampsia

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OBJECTIVES/GOALS: Low-dose aspirin is an established treatment to prevent preeclampsia, a leading cause of maternal and perinatal complications. Nevertheless, aspirin failure is not uncommon. We are investigating whether a gain-of-function genetic polymorphism in a platelet thrombin receptor is associated with aspirin failure in the prevention of preeclampsia. METHODS/STUDY POPULATION: Women who had preeclampsia in an initial pregnancy who then received low-dose aspirin in a subsequent pregnancy will be evaluated. We will compare between women who developed preeclampsia despite aspirin (aspirin non-responders) to women who did not develop preeclampsia with aspirin treatment (aspirin responders). Specifically, we will evaluate the allelic frequency of a single nucleotide variant (rs773902) in PAR4 thrombin receptor on platelets. This variant is associated with increased platelet function and potentially aspirin resistance. In addition, we will analyze the platelet response to PAR4 activation before and 1 hour after administering a single 81 mg enteric-coated aspirin tablet. RESULTS/ANTICIPATED RESULTS: We hypothesize that the prevalence of the PAR4 variant will be significantly higher among women who had recurrence of preeclampsia despite aspirin therapy. We also postulate that women who developed preeclampsia despite aspirin prophylaxis and have the polymorphism will have increased platelet aggregation in response to activation of PAR4, either by thrombin or peptides that activate the receptor, both at baseline and 1 hour after aspirin administration. DISCUSSION/SIGNIFICANCE: If our hypothesis that aspirin failure in preeclampsia prevention is associated with the gain-of-function polymorphism in the platelet PAR4 thrombin receptor, there may be justification for additional experimental studies to assess whether better pregnancy outcomes can be obtained by targeting thrombin itself using low molecular weight heparin.

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Genomic and Immunologic Characterization of Lung Adenocarcinoma in Never Smokers vs. Smokers*

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OBJECTIVES/GOALS: Smoking is a well-established risk factor for lung cancer, but never smokers account for up to 25% of lung cancer cases. There is mounting evidence that lung cancer in never smokers is biologically distinct. We aim to characterize the genomic and immunologic features of lung adenocarcinoma in never smokers versus smokers. METHODS/STUDY POPULATION: We examined clinical, genomic, and bulk-RNA sequencing data from 499 patients in the TCGA lung adenocarcinoma cohort. Tumor mutation burden was analyzed using maftools (R package). Tumor immune characterization was completed using CIBERSORTx, a digital cytometry tool that uses single cell reference profiles to determine immune cell type frequencies from bulk-RNA sequencing data. Single cell reference profiles for 19 different immune cell types were constructed from sequencing of freshly resected lung tumor tissue from UCSF patients. Partitioning Around Medoids (PAM; R package) was used to identify distinct immune phenotypes based on immune cell composition. Fisher's exact test was used to evaluate for associations between immune phenotypes and smoking status. RESULTS/ANTICIPATED RESULTS: Of the 499 TCGA lung adenocarcinoma patients, 75 were never smokers, 269 were female, and 246 were over the age of 65. Never smokers had lower tumor mutation burden and lower predicted neoantigen burden compared to smokers ($p < 0.001$). There was no difference in total tumor immune cell infiltration between never smokers and smokers. PAM yielded 2 distinct clusters/immune phenotypes. The first was enriched in M1 Macrophages, cytotoxic T Cells, helper T Cells, regulatory T Cells, and Plasma Cells. The second was enriched in plasmacytoid Dendritic Cells, M2 Macrophages, and exhausted cytotoxic T Cells. Never smoking status was associated with an increased odds of having the first immune phenotype (OR 1.95, 95% CI: 1.15 - 3.35) and this association was statistically significant ($p = 0.0086$). DISCUSSION/SIGNIFICANCE: Our findings suggest that never smokers have an immune phenotype that is distinct from that observed in smokers. The distinct immune characteristics we observed could explain clinical trial data suggesting immune checkpoint inhibitors are less effective in never smokers and hold implications for tailoring therapy.

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Harnessing the potential of transcriptional adaptation as a mechanism for Amyotrophic lateral sclerosis

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OBJECTIVES/GOALS: Understanding the mechanism of transcriptional adaptation may contribute to an explanation for variation in clinical manifestations of Amyotrophic lateral sclerosis patient phenotypes. METHODS/STUDY POPULATION: To examine transcriptional adaptation, we utilized gene editing tools in HT1080 cells and patient samples with known CHCHD10 mutations causative for Amyotrophic lateral sclerosis. Frameshift mutations were performed via CRISPR-Cas9. Ribonucleoprotein electroporation was used to transfect cells and DNA sequencing was conducted to validate gene editing. To validate transcriptional adaption, changes in levels of protein and gene expression will be measured via immunoblot and quantification of CHCHD10 and CHCHCD2 from whole cells lysates of the edited cells. RESULTS/ANTICIPATED RESULTS: We anticipate that CHCHD2 transcriptional adaptation can functionally compensate for the locus loss of function of CHCHD10. This mechanism of transcriptional adaptation may contribute to an explanation for variation in clinical manifestations of patient phenotypes. DISCUSSION/SIGNIFICANCE: Our approach would advance discovery science towards by exploring CHCHD10/2 transcriptional adaptation mechanism that can lead to novel therapies for rare Amyotrophic lateral sclerosis, such as CHCHD10-R15L.

https://doi.org/10.1017/cts.2023.344