Molecular pathology selected abstracts

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Study of a newborn with atypical hemolytic uremic syndrome

Augstus 2023—Atypical hemolytic uremic syndrome is a rare, potentially life-threatening thrombotic microangiopathy. The disorder causes tiny blood clots to form in blood vessels and results in organ damage. Clinical findings in atypical hemolytic uremic syndrome (aHUS) include hemolytic anemia, low platelet count, and acute kidney failure. In many cases, HUS is caused by Shiga toxin-producing *E. coli*, other infections, or certain medications, or it can result from other health conditions. The label "atypical" is used to delineate hemolytic uremic syndrome that is not due to any of these common causes. Research shows that dysregulation of the complement system is a major contributor to the clinical manifestations of aHUS. The complement system is an important component of the innate immune defense system, which is the body's first line of defense against pathogens. It is made up of multiple plasma proteins that opsonize foreign targets and induce inflammatory responses to fight infection, and it can assemble into a membrane-attack complex to puncture the membrane of targeted cells. The complement system is also a highly regulated noncellular system for preventing lysis of host cells. Dysregulation of the complement system can result in inadvertent attacks on host endothelial cells, resulting in endothelial cell damage, formation of microthrombi, consumption of platelets, mechanical disruption of red blood cells, and organ damage characteristic of aHUS. Loss-of-function alterations in genes that encode components regulating the complement system and gain-of-function alterations in genes that encode complement activators have been identified in patients with aHUS. Because aHUS is usually triggered by an environmental agent or health condition, these genetic aberrations are considered risk factors for developing the disease. While genetic abnormalities are seen in some cases of aHUS, 30 to 50 percent of cases have no known underlying genetic alteration. The authors of this study described a clinical case involving a newborn boy with aHUS who was responsive to anticomplement antibody treatment. Whole exome sequencing identified a de novo germline missense mutation in *C1GALT1C1*:c.266 C>T,p.(T89I) on chromosome X. Other laboratory studies of the patient were negative for HUS-associated infections, defects in other aHUS-associated genes, and significant copy number variations. *C1GALT1C1* encodes the protein C1GALT1C1, known as Cosmc. This protein is a key component of the glycosylation pathway and adds galactose to the GalNac monosaccharide on serine or threonine residues to form the T antigen. Normally, other enzymes then add other sugar moieties to this highly immunogenic T antigen. However, in certain disease states, the T antigen becomes exposed, is detected by the immune system, and triggers the complement cascade resulting in HUS. Laboratory testing showed that the patient's *C1GALT1C1* mutation resulted in a persistently exposed T antigen, even during treatment with anticomplement antibody therapy. The study findings not only identify a novel mutation in a potentially devastating, yet treatable, rare disease, but they re-emphasize the dangers surrounding the production of neoantigens in disease and raise further questions about complement activation for patient-tailored therapeutic intervention.

Hadar N, Schreiber R, Eskin-Schwartz M, et al. X-linked *C1GALT1C1* mutation causes atypical hemolytic uremic syndrome. *Eur J Hum Genet*. 2023. https://doi.org/10.1038/s41431-022-01278-5

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Contribution of air pollutants to lung adenocarcinoma

Lung cancer is a leading cause of cancer death. Although traditionally associated with smoking, a large proportion of patients with lung cancer are nonsmokers, and lung cancer epidemiology, histology, and mutational profiles differ between smokers and nonsmokers. Risk factors for lung cancer include environmental exposures, radiation exposure, endocrine factors, personal history of lung disease, and family history of lung cancer. Environmental particulate matter (PM) measuring 2.5 µm ($PM_{2.5}$) or less is an established risk factor for lung cancer. However, the cellular mechanisms involved in this specific lung cancer pathogenesis are only beginning to be understood. The authors explored the association between particulate matter and lung cancer through epidemiological studies and in vivo and in vitro studies to provide a mechanistic explanation of how air pollution contributes to lung cancer. Epidemiological studies were performed using datasets of $PM_{2.5}$ air pollution from England, South Korea, and Taiwan, and these were correlated with the estimated incidence of *EGFR*-mutated lung carcinomas. (*EGFR* is the most common driver mutation in nonsmoker lung cancer.) The data showed a consistent relationship between $PM_{2.5}$ and estimated EGFR-driven lung cancer, with high $PM_{2.5}$ exposure being a significant risk factor for such cancer. To explore the biology of how particulate matter contributes to lung cancer, mouse models of lung cancer with doxycycline-inducible *EGFR* mutations were exposed to particulate matter or saline, and tumor growth was assessed for the cell types involved, gene expression profiles, and biomarker expression. Mice exposed to particulate matter had increased inflammatory response, increased influx of macrophages, alveolar type II epithelial cells, and tumor cell burden, as compared to control mice. The immune response was shown to be an important factor in developing particulate matter-mediated *EGFR*-mutated lung carcinoma, as immune-deficient mice did not develop cancer to the same extent as immune-competent mice. Mouse lung epithelial cells exposed to $PM_{2.5}$ showed different gene-expression patterns than epithelial cells from control mice exposed to only saline. Moreover, functional studies using a three-dimensional lung-organoid model showed that particulate matter exposure in the context of a genetically susceptible background (*EGFR* driver mutation) can reprogram cells to a lung progenitor state. Finally, the authors investigated whether driver mutations in *EGFR* and *KRAS* genes could be found in noncancerous human lung tissue, as advances in the mutational profiling of various cancers have occasionally identified low-level incidental pathogenic driver mutations in the genes of patients who were not diagnosed with cancer. Driver mutations in *EGFR* and *KRAS* were seen in 18 and 53 percent of noncancerous lung tissue samples, respectively, and a significant correlation in mutation count and age was also seen. The presence of mutations in noncancerous tissue suggests a genetically altered state susceptible to further tumorigenesis and progression. The authors provided epidemiological data that showed increased *EGFR*-mutant lung cancer incidences with increased $PM_{2.5}$ levels and a cellular basis for how air pollution particulate matter alters the host environment. In a genetically susceptible host (that is, one with an *EGFR* mutation), particulate matter-induced inflammatory changes due to increased macrophages, cytokine activity, and transcriptional alteration of alveolar epithelial cells promote clonal growth and proliferation. These studies provide support for clinically targetable treatment options and reducing air pollutants to improve public health.

Hill W, Lim EL, Weeden CE, et al. Lung adenocarcinoma promotion by air pollutants. *Nature*. 2023;616:159–167.

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