Molecular pathology selected abstracts

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Ability of genetic alterations to predict development of acute myeloid leukemia

September 2018—Acute myeloid leukemia affects more than 60,000 people in the United States every year and has a mortality rate of more than 90 percent. It is the most common form of acute leukemia and is caused by unchecked growth of immature precursor cells in the bone marrow. These immature cells, or blasts, are myeloid precursors that often develop into dysfunctional, cancerous white blood cells that fill the bone marrow and spread into the blood. Acute myeloid leukemia (AML) can also produce immature, cancerous red blood cells and platelets. Therefore, several subtypes of AML exist that are defined by the type of cell produced. As the blasts increase in number, these cells crowd out the normal bone marrow and result in numerous medical problems, including fever, an inability to fight infection, easy bruising, and fatigue. The average age of patients with AML is 68 years, with most patients older than 45 years at diagnosis. AML appears to be caused by a clonal expansion of hematopoietic cells that have acquired somatic mutations in a subset of genes. Clonal hematopoietic changes occur in approximately 10 percent of people older than 65 years of age. This has been associated with cardiovascular disease and an increased risk of AML. However, understanding which alterations in clonal hematopoiesis cause AML has been problematic due to the relatively low number of at-risk patients in the overall population who can be studied and the limited number of longitudinal studies in at-risk patients. Two recent studies suggest that mutations may occur at least one year, and up to 10 years, prior to disease onset and that certain mutations may predict disease development and rapidity of disease onset. In a study by Desai, et al. (*Nat Med.* 2018;24:1015–1023), the authors performed deep sequencing of serial peripheral blood samples collected from 212 women in the Women's Health Initiative clinical trial who ultimately developed AML. At the time the samples were collected, the study subjects were healthy and were being prospectively followed to test the effects of hormonal therapy on postmenopausal health. These DNA samples were compared with DNA from an equal number of age-matched controls in the study who did not develop AML. Using whole exome sequencing, the authors determined that mutations in *IDH1, IDH2, TP53, DNMT3A, TET2*, and spliceosome genes were associated with an increased risk of developing the disease. In all cases, mutations in *IDH1, IDH2,* and *TP53* were associated with AML development. Study subjects who eventually developed AML also showed greater clonal complexity (increased clone size and higher number of mutations) than matched controls and were more likely to have a variant allele frequency of greater than 10 percent. In the subset of study subjects who had serial blood draws, the investigators discovered that mutations accumulated over time and that the rapidity of *IDH2* or *TP53* gene mutation correlated with a shorter time to AML development. The results from the study were complemented by another recent study by Abelson, et al. (*Nature.* 2018;559:400–404), in which the authors examined blood samples collected during a six-year period prior to the diagnosis of AML. Similar to the findings in Desai, et al., the second study found that mutations in *TP53* and genes associated with splicing appeared to be important in predicting AML development. Taken together, these studies suggest that the likelihood of developing AML may be predictable during an extended preclinical phase of disease development using peripheral blood samples. Therapies to target and correct *IDH2* mutations have been developed. Additional drug-based therapies to address pathway alterations may prove beneficial in targeting altered cells well before the development of AML.

Desai P, Mencia-Trinchant N, Savenkov O, et al. Somatic mutations precede acute myeloid leukemia years before diagnosis. *Nat Med.* 2018;24:1015–1023.

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Abelson S, Collord G, Ng SWK, et al. Prediction of acute myeloid leukemia risk in healthy individuals. *Nature.*

2018;559:400–404.

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Link between Alzheimer disease and antiviral response to herpesvirus

A major area of investigation in Alzheimer disease has focused on the deposition of amyloid-β peptide as β-amyloid plaques in the brain. The amyloid-β peptide historically has been considered a byproduct of brain catabolism, with aberrant deposition in brain tissue resulting in Alzheimer disease (AD). However, recent data support an alternate hypothesis that suggests that the amyloid-β peptide serves an important, protective immune role in the brain due to its antiviral and antibacterial properties. Similar to other antimicrobial peptides, amyloid-β is evolutionarily conserved in vertebrates and can form soluble oligomers that damage microbial cell membranes and eliminate endotoxins and other pathogens in the brain. However, overactivation of this pathway in response to infection may lead to ongoing neuroinflammation, deposition of plaques, and AD. In the past decade, numerous studies have identified links between neuroinflammation, infectious agents such as herpes simplex 1 (HSV-1), and amyloid plaque formation. Two recent articles have further evaluated the human herpesvirus family relative to the development of AD. The first study (Readhead B, et al. *Neuron.* 2018;99:64–82) applied multiscale network modeling of the late-onset AD-associated virome, integrating genomic, transcriptomic, proteomic, and histopathological data obtained from four regions of the postmortem brain. The authors constructed a pathway map in preclinical AD by analyzing neuronal gene-expression data in areas of the brain with significant neuronal loss and compared this with data from normal, healthy control brains. Virus-mediated network activities, including expression of viral infection susceptibility risk genes, were increased in preclinical AD patients. The authors then evaluated differential virus abundance in AD and identified increased human herpesvirus 6A and 7 (HHV-6A and HHV-7, respectively) in multiple brain regions in AD patients, which was confirmed in two additional independent cohorts. Both increased viral levels and patient DNA variant levels linked to viral infection were associated with increased plaque production, which appears mediated through miR-155 regulation. In another article in the same issue of *Neuron* (pp. 56–63), Eimer, et al., showed that oligomers derived from the amyloid-β peptide can bind to glycoproteins present on herpesvirus. Binding of these glycoproteins could protect mice against herpes-induced encephalitis and prevent HSV-1 infection of human nerve cells in culture. Cell-surface binding to HSV-1, HHV-6A, and HHV-6B resulted in the rapid development of fibrillary structures attached to the viral envelope, ultimately with sequestration of virus particles in insoluble plaques. Taken together, these data suggest that the amyloid-β peptide undergoes oligomerization to protect the brain against infection with herpesvirus family members. However, ongoing response in this context may lead to amyloid plaque deposition and development of AD. Understanding the critical elements that regulate the switch from innate immune protection to overactive pathogenic deposition of amyloid plaques will be critical in defining risk and possible treatment methods for AD.

Readhead B, Haure-Mirande JV, Funk CC, et al. Multiscale analysis of independent Alzheimer's cohorts finds disruption of molecular, genetic, and clinical networks by human herpesvirus. *Neuron.* 2018;99:64–82.

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Eimer WA, Kumar DKV, Shanmugan NKN, et al. Alzheimer's disease-associated β-amyloid is rapidly seeded by Herpesviridae to protect against brain infection. *Neuron.* 2018;99:56–63.

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