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Age-related DNA methylation and hemostatic factors

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In this issue of *Blood*, a study by Ward-Caviness et al identifies a significant relationship between age-related DNA methylation changes and thrombotic risk in the elderly. They studied the relationship between hemostatic factors and 3 epigenetic measures of aging: extrinsic epigenetic age acceleration difference (EEAD), intrinsic epigenetic age acceleration difference (IEAD) for blood-specific measures, and age acceleration difference (AAD) to assess differences between epigenetic and chronological age in nonblood tissues.[1]

IEAD is a blood-specific measure of aging that adjusts the standard tissue agnostic measure[2] for blood immune cells such as naïve $CD8^+$ T cells, plasma B cells, and $CD4^+$ T cells among others.[3] EEAD is calculated by weighing the global epigenetic age measured by imputed blood immune cell counts and is designed to track aging of the immune system as assessed by DNA methylation changes. The difference term in IEAD and EEAD refers to taking the difference between the epigenetic aging measures and chronological age. The differences between these 2 ages are associated with outcomes such as mortality and may also indicate accelerated aging.[4] The cell counts for these 2 measures were estimated on the basis of methylation data using approaches by Houseman et al[5] and by Horvath and Ritz.[6] AAD is an estimation of biological age derived from methylation data, and it is strongly correlated with chronological age.[7] In their article, the authors showed that AAD and IEAD are strongly correlated in blood when using the Horvath and Ritz measure of epigenetic age[7] as opposed to the Houseman et al measure.

The analyses were performed using data from 11 studies from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Hemostasis Working Group,[8] which included multiple racial participants with hemostatic factors and clotting time measures. The authors used random-effect meta-analysis to investigate the association between measures of epigenetic aging and hemostatic factors plus measures of clotting time. The hemostatic factors of interest included fibrinogen, plasminogen activator-inhibitor 1 (PAI-1), D-dimer, factor VII, von Willebrand factor, and activated partial thromboplastin time. Two models were used for the analyses. The first (basic) model was adjusted for chronological age[2] and sex. The adjustment for age and age squared was to model the linear failure rate during the individual's prime age, followed by a rapidly increasing failure rate as the individual gets older. The second (full) model adjusted for the basic model plus body mass index, physical activity, and smoking status. The basic model was the primary model because not all the cohorts had complete information for the full model. For the cohorts with family data only, the probands were included in the analysis. Some cohorts had multiple hemostatic measures, and others had a single measure with data for only a single time point DNA methylation. The R package metafor was used for the meta-analysis, and a minimum of 3 cohorts with hemostatic factors was required. Except for PAI-1, data were available from cohorts with European or African ancestry. Only fibrinogen factor was available for European and African ancestries in at least 3 cohorts, and random effect meta-analysis was performed to account for the heterogeneity of the cohorts. For all other analyses, a fixed effect meta-analysis was used.

Fibrinogen and PAI-1 are well-known risk factors for multiple adverse cardiovascular outcomes; therefore, because the hemostatic factors measures are associated with age, it is possible that age-related biological mechanisms influence the regulation and concentration of hemostatic factors. The study results showed that older epigenetic age compared with chronological age is associated with higher concentrations of fibrinogen and PAI-1 and decreased clotting time. This indicates that these associations are similar to the alterations in the hemostatic profile seen with advancing age.

This study is the first to assess the relationship between epigenetic aging biomarkers and hemostatic factors. It could lead to a better understanding of the mechanisms involved in accelerated epigenetic aging that underlay the association between alterations in the hemostatic profile and aging. This has the potential to reveal novel mechanisms of hemostatic regulation.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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