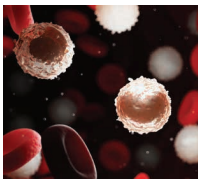
Hematopoiesis

Major Finding: Genetic drivers of clonal hematopoiesis (CH) predict risk of myeloid and lymphoid malignancies.

Concept: CH can be divided into myeloid and lymphoid subtypes that can predict lineage-specific disease.

Impact: This work highlights genetic abnormalities that identify those at risk of hematologic malignancies.

LINEAGE-SPECIFIC CLONAL HEMATOPOIESIS PREDICTS HEMATOLOGIC MALIGNANCY



Clonal expansion of blood cells, known as clonal hematopoiesis, results from somatic mutations in blood cells and can occur in healthy individuals, with prevalence increasing with age. Clonal hematopoiesis with indeterminate potential (CHIP) refers to when alterations arise in genes recurrently mutated in hematologic malignancies. Previous CHIP studies have focused on variants in genes mutated in myeloid malignancies, reporting an association between CHIP and risk of these diseases. To explore whether clonal hematopoiesis can also contribute to risk of lymphoid malignancies, Niroula and colleagues analyzed somatic variants in myeloid and lymphoid driver genes in whole-exome sequencing data of individuals in the UK Biobank (UKB) ages 40 to 70 years with no previous hematologic malignancy (n = 46,706), defining a list of genes recurrently mutated in lymphoid malignancies (L-CHIP) and a list of genes known to drive CHIP and myeloid malignancies (M-CHIP). L-CHIP was associated with higher incidence of lymphoid malignancies diagnosed between 6 months and 12 years following initial recruitment into the UKB, whereas M-CHIP was associated with higher incidence of myeloid malignancies, revealing a distinct lineage specificity. Given that mosaic chromosomal alterations (mCA) have been associated with risk of lymphoid malignancies, mCAs identified from the SNP-array intensity data from the UKB (n = 400,452) were analyzed to determine whether myeloid- and lymphoid-specific mCAs were similarly associated with risk of lineage-specific malignancies. Indeed, myeloid mCAs increased risk of myeloid malignancies, whereas lymphoid mCAs increased risk of lymphoid malignancies. Moreover, specific types of clonal hematopoiesis were associated with subtypes of myeloid and lymphoid malignancies, with L-CHIP and lymphoid mCAs strongly connected with chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL). Notably, incorporating the presence of abnormal peripheral blood counts with the presence of lineage-specific CHIP and mCAs increased power to predict risk of developing myeloid malignancies and CLL/SLL. In summary, this work highlights the potential clinical utility of integrating analysis of genetic alterations and peripheral blood counts to identify individuals at risk of developing specific hematologic malignancies. ■

Niroula A, Sekar A, Murakami MA, Trinder M, Agrawal M, Wong WJ, et al. Distinction of lymphoid and myeloid clonal hematopoiesis. Nat Med 2021;27:1921–7.

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Tumorigenesis

Major Finding: Glycogen is a key oncogenic metabolite in liver tumor initiation.

Concept: Glycogen undergoes liquid–liquid phase separation and aggregates with MST1/2, inhibiting the Hippo pathway.

Impact: Glycogen storage plays an unappreciated role in signal transduction and the promotion of cancer initiation.

GLYCOGEN ACCUMULATION INDUCES THE HIPPO PATHWAY AND LIVER TUMORIGENESIS

To support tumor growth, cancer cells typically increase their consumption of glucose. Excess glucose is primarily stored as glycogen in the liver and muscles, and loss-of-function mutations in enzymes involved in glycogenolysis contribute to many human diseases, but the mechanisms behind how glycogen and its metabolism contribute to cancer remains to be fully elucidated. Liu, Li, Zhang, Xiao, Zhang, and colleagues investigated the role of glycogen in tumor initiation in the liver, finding that there is an accumulation of glycogen in early-stage hepatic tumors. Longitudinal analysis of glycogen content at different stages of tumor development indicated that these elevated amounts at early tumor stages are then reduced at later stages of disease development. RNA-sequencing analysis suggested that this effect was mediated by glucose-6-phosphatase (G6PC) downregulation, which catalyzes the last step of glycogenolysis, and a liver-specific knockout of G6PC, as well as of *Pygl* which encodes a liver glycogen phosphorylase enzyme that breaks down glycogen, displayed an increase in liver size and proliferation. This phenotype mimics the increased organ size observed in Hippo pathway–deficient mice. Loss of G6PC in the liver led to diminished activity of MST1/2, a critical kinase in the Hippo pathway, which then enhanced YAP activity through reduction in its phosphorylation and subsequent increase in its nuclear localization and activation of target genes. Additionally, a contributing factor to the reduction in MST1/2 activity was found to be the formation of MST1/2–glycogen aggregates. Glycogen was observed to undergo liquid–liquid phase separation, which supports the retention of MST1/2 and was mediated by Laforin, a protein previously found to interact with glycogen. Moreover, further experiments indicated the requirement for glycogen storage in hepatic tumor formation, as an increase in glycogen storage through liver-specific deletion of *G6pc* accelerated liver tumorigenesis whereas its reduction by *Gys2* (a glycogen synthase) deletion decreased liver tumor incidence. Overall, these findings point to a critical role of glycogen storage in cell signaling and cancer initiation and implicate its potential importance in early detection and intervention. ■

Liu Q, Li J, Zhang W, Xiao C, Zhang S, Nian C, et al. Glycogen accumulation and phase separation drives liver tumor initiation. Cell 2021;184:5559–76.

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