LOSS OF COHESIN COMPLEX ALTERS EARLY CELL PROLIFERATION AND GENE EXPRESSION IN CORE BINDING FACTOR ACUTE MYELOID LEUKEMIA

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Background: Core binding factor acute myeloid leukemia (CBF-AML), defined by inv(16) or t(8;21) lesions, is considered a favorable risk disease yet carries a 30% relapse rate. The oncofusion proteins CBFβ-SMMHC and RUNX1-RUNX1T1 produced by inv(16) and t(8;21), respectively, repress the function of the CBF complex leading to maturation arrest in myeloid cells. Mutations in cohesin complex genes occur commonly in t(8;21) AML but never occur in inv(16) AML, suggesting that cohesin complex interacts with each CBF fusion protein in a distinct way to affect leukemogenesis. We hypothesize that loss of cohesin complex function cooperates with RUNX1-RUNX1T1 to enhance leukemogenesis but inhibits leukemogenesis driven by CBFβ-SMMHC via altered chromatin state and critical gene expression changes.

Materials/Methods: We transduced wild type (Smc3+/+) or cohesin deficient (Smc3+/-) murine bone marrow with retrovirus expressing GFP, RUNX1-RUNX1T19a-GFP, or CBFβ-SMMHC-GFP. A portion of transduced cells were plated in methylcellulose with cytokines to assess colony-forming capacity, colony size, morphology, and replating ability. RNA was isolated from cells, and RTqPCR was performed for hematopoietic regulator genes. A portion of cells were transplanted into lethally irradiated recipients for in vivo leukemia modelling.

Results: Cells expressing RUNX1-RUNX1T19a showed increased colony size and number in Smc3+/- cells compared to Smc3+/+, whereas cells expressing CBFβ-SMMHC showed decreased colony size and number in Smc3+/- cells. Cohesin deficiency alone did not alter colony size or number. Cohesin deficient cells demonstrated altered expression of key hematopoietic regulator genes in all conditions, though expression patterns varied in each group. RUNX1-RUNX1T19a induces similar, transplantable, leukemias in both Smc3+/+ and Smc3+/- cells in ongoing in vivo experiments.

Conclusions: Cohesin deficiency enhances the growth of RUNX1-RUNX1T19a expressing bone marrow cells while it decreases the growth of CBFβ-SMMHC expressing cells in pre-leukemic models. Loss of cohesin also leads to altered gene expression of hematopoietic regulators with patterns unique to cohesin loss alone or in the presence of each CBF fusion protein. These results support the hypotheses that loss of cohesin cooperates with RUNX1-RUNX1T1 to enhance leukemogenesis but prevents leukemogenesis in cells expressing CBFβ-SMMHC. Ongoing murine leukemia models and human cell line studies will further define how cohesin interacts with CBF fusion proteins.