1492 CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL ALTERS SOLID TUMOR MICROENVIRONMENT AND OUTCOMES IN TRIPLE NEGATIVE BREAST CANCER

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Background Clonal hematopoiesis of indeterminate potential (CHIP) is characterized by blood cells with somatic mutations in leukemia-associated genes in patients without hematologic malignancies. The incidence of CHIP increases with age, and it is associated with both an increased risk of transformation to myeloid neoplasms and cardiovascular disease. There is growing evidence that CHIP is associated with aberrant inflammatory signaling and increased risk or poor outcomes in a wide range of diseases. Given that CHIP is a phenomenon of hematopoietic cells, we hypothesized that CHIP alters the immune response to solid tumors by dysregulating tumor-infiltrating leukocytes. Indeed, CHIP mutations have been identified in tumor-infiltrating leukocytes, and observational studies have reported an association between CHIP and decreased overall survival among patients with solid tumors. Patients with solid tumors also have an increased incidence of CHIP, driven in part by chemotherapy and radiation.

Methods Using triple negative breast cancer (TNBC) as a model, we investigated the impact of CHIP on tumor progression and the functional effects of CHIP mutations on tumor-infiltrating leukocytes. We generated two murine models of CHIP representing the most commonly mutated genes, *Dnmt3a* and *Tet2*. Following bone marrow transplantation, wild type and mutant-bearing immune cells are marked by different CD45 isoforms. The resulting mice were injected with an orthotopic, syngeneic TNBC model. Tumor growth was measured regularly until tumors reached endpoint. Immune cells from peripheral tissues and tumor infiltrate were then phenotyped using flow cytometry.

Results Mice with CHIP displayed increased tumor growth and aberrant inflammatory signaling compared to control mice. Tumor-infiltrating immune cells displayed different phenotypes compared to peripheral blood, with the greatest difference observed in myeloid lineages. These results support the hypothesis that CHIP mediates differential outcomes in solid tumors via altered immune cell function. They further support the need for additional mechanistic and translational studies into the relationship between CHIP and solid tumors.

Conclusions Investigating the complex interplay between CHIP and solid tumors may contribute to a better understanding of the implications of CHIP, provide insight into the tumor immune microenvironment, and identify strategies to manage and treat patients with solid tumors.

Ethics Approval All mouse studies obtained appropriate ethics approval from the VUMC Animal Care and Use Program, in accordance with IACUC standards.

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