Cancer Research Foundation Young Investigator Award Final Report
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Project: "Characterizing the contribution of mutations in cancer predisposition genes to therapy-related myeloid neoplasms"

Aims:
Aim 1: Determine the prevalence of deleterious germline mutations in genes involved in hereditary susceptibility to breast and ovarian cancer in a cohort of patients who developed therapy-related leukemias after treatment for breast cancer

Aim 2: Test if *Brca1*-deficiency contributes to abnormalities in hematopoiesis and to the development of therapy-related leukemias *in vivo* a) spontaneously or b) after cytotoxic exposures

Brief Background:
Leukemias that develop after a person has received chemotherapy or radiation for another cancer are called "therapy-related" leukemias (t-MNs). Most patients with a t-MN will die of this disease within an average of 8 months' time. Breast cancer survivors now account for the largest number of cancer related cases of t-MNs. Risk factors for t-MN development remain unclear. The goal of this work was to begin to understand if inherited cancer susceptibility gene mutations contribute to t-MN risk among breast cancer survivors.

Brief methods and results:
Aim 1: I identified 88 women with therapy-related leukemia after breast cancer seen at The University of Chicago. I performed gene panel-based sequencing of 47 who had available germline DNA samples and identified germline damaging mutations in 19 (22%) in the following genes: *BRCA1* n=3, *BRCA2* n=2, *TP53* n=3, *CHEK2* n=1, *PALB2* n=1. Further, 57% of women with therapy-related leukemia had close relatives with cancers often associated with hereditary cancer syndromes. This data provides further support that inherited cancer susceptibility genes play a role in therapy-related leukemias. Whether the leukemias are directly related to the prior chemotherapy/radiation in all cases or whether some are unrelated (i.e., would have happened regardless of prior therapy) deserves further study.

Aim 2: To functionally test whether one of these genes, *Brca1*, is critical for hematopoiesis, I developed a conditional mouse model of Brca1 deficiency in the bone marrow. I demonstrated that the majority of mice lacking Brca1 in their hematopoietic tissues develop spontaneous bone marrow failure and/or leukemias or lymphomas by six months of age. I showed that the hematopoietic stem and progenitor cells from these mice are less able to regenerate normal hematopoiesis after transplantation into another mouse. Further, they feature genomic instability and hypersensitivity to DNA crosslinking chemotherapy. These are the hallmark features of Fanconi anemia (FA). Thus, this work provided strong evidence that Brca1 is critical for hematopoiesis and is a bona fide FA-like gene. This mouse model serves as a model system in which to understand Brca1 function and model the human disease, FA. The effects of cytotoxic exposures on this model system are ongoing.

Resulting Publications:

1. **Churpek JE**, Marquez R, Claussen K, Neistadt B, Lee MK, Churpek MM, Hou D, Weiner H, Bannerjee M, Godley LA, Le Beau MM, Pritchard CC, Walsh T, King M-C, Olopade OI, and Larson RA. Inherited mutations in cancer susceptibility genes are common among breast cancer survivors who develop therapy-related leukemia. *Cancer.* 2016 Jan 15;122(2):304-11. PMID: 26641009. NOTE: This publication had an accompanying invited editorial, highlighting the impact of this work.

2. Vasanthakumar A, Arnovitz S, Marquez R, Lepore J, Rafidi G, Asom A, Weatherly M, Davis EM, Neistadt B, Duszynski R, Vardiman JW, Le Beau MM, Godley LA and **Churpek JE**. *Brca1* deficiency causes bone marrow failure and spontaneous hematologic malignancies in mice. *Blood.* 2016 Jan 21;127(3):310-3. PMID: 26644450. Selected for an oral presentation at The American Society of Hematology Annual Meeting 2015.

Impact on my career:

This work formed the foundation for my successful NIH K08 Mentored Clinical Scientist Award (funded 9/2015) and for an upcoming R01 application. This work contributed to an American Society for Clinical Investigation Young Physician Scientist Award (2016). This work has helped establish my career as a translational cancer geneticist.

Impact on science:

This work established *Brca1* as a new gene with critical importance to bone marrow function and provides rationale to offer hereditary breast and ovarian cancer genetic testing to all women with t-MN after breast cancer.