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An Integrative Genomics Approach for Associating Genetic Susceptibility with the Tumor Immune Microenvironment in Triple Negative Breast Cancer

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Abbreviations: TNBC : Triple Negative Breast Cancer; ER: Estrogen Receptor; PR: Progesterone Receptor; HER-2: Human Epidermal Growth Factor; GWAS: Genome Wide Association Studies; SNPs: Single Nucleotide Polymorphisms; GEO: Gene Expression Omnibus; FDR: False Discovery Rate; IPA: Ingenuity Pathway Analysis, GO: Gene ontology

ABSTRACT

Background: Triple-negative breast cancer (TNBC) is the most aggressive form of breast cancer. It is a heterogeneous disease with poor prognosis. Contributing to the worse prognosis in TNBC is the higher rates of relapse and rapid progression to metastatic disease which is often lethal. With the exception of cytotoxic chemotherapy, there is currently no effective targeted therapies. Immunotherapy such as vaccines offer new opportunities for treatment of TNBC. But realizing the potential of immunotherapy and vaccination may require understanding the association between the tumor immune microenvironment and genetic susceptibility to TNBC. The objective of this exploratory study was to investigate the potential association between genetic susceptibility and tumor immune microenvironment in TNBC.

Methods: We integrated information on genetic variants and genes associated with an increased risk of developing breast cancer with gene expression data from the Caucasian women diagnosed with the basal-like immune activated (N=54) and basal-like immune suppressed (N=60) subtypes of TNBC to discover and characterize immune modulated gene signatures, molecular networks and biological pathways enriched for genetic susceptibility variants.

Results: The investigation revealed immune modulated gene signatures, molecular networks and biological pathways enriched for genetic susceptibility variants. The discovered pathways included the role of BRCA1 in DNA damage response, hereditary breast cancer, aryl hydrocarbon receptor and molecular mechanisms of cancer signaling pathways.

Conclusion: The investigation suggests the link between genetic susceptibility and the tumor immune microenvironment in TNBC and establishes putative functional bridges between genetic predisposition and immune modulated pathways.

Introduction

Triple-negative breast cancer (TNBC) represents a diverse group of breast cancers that are characterized by lack of expression of the estrogen receptor (ER), progesterone receptor (PR) and lack of amplification of the human epidermal growth factor (HER2) [1-2]. It is a heterogeneous disease representing 15–20 % of all new breast cancers diagnosed each year in the US women population and accounting for 25% of all breast cancer related deaths annually [3]. Well known risk factors include age, ethnicity and genetics. TNBC has high prevalence in younger premenopausal women, primarily African American women and BRCA1 mutation carriers [1]. The lack of ER and PR expression and the lack of HER-2 amplification has significantly reduced targeted treatment options for patients with TNBC [1]. Currently, cytotoxic chemotherapy remains the main therapeutic modality [1]. Data from many studies over the past two decades has shown significant benefit of chemotherapy in the neoadjuvant, adjuvant and metastatic settings [4]. However, the