Perturbations in Neuroinflammation-Related Pathways in Chronic Paclitaxel-Induced Peripheral Neuropathy in Breast Cancer Survivors

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Background and Purpose

The prevalence of chemotherapy-induced peripheral neuropathy (CIPN) in cancer survivors is as high as 60%. CIPN is the most debilitating symptom reported oncology patients and can lead to treatment discontinuation. No interventions are available to treat CIPN. A critical barrier to the development of efficacious interventions is the lack of understanding of the mechanisms underlying CIPN. In this pilot study, we used a systems biology approach to evaluate the molecular characteristics associated with paclitaxel-induced peripheral neuropathy (PIPN). PIPN is associated with neuroinflammatory (NI) mechanisms in pre-clinical studies.

The objective of this pilot study was to compare gene expression patterns between breast cancer (BC) survivors with and without PIPN with a focus on neuroinflammatory-related processes.

Methods

Of the 1450 cancer survivors who were screened, 754 were enrolled, and 623 completed the self-report questionnaires and the study visit in the Parent grant (R01 CA151692). The National Coalition for Cancer Survivorship's definition of cancer survivor was used in this study (i.e., a person is a cancer survivor from the moment of diagnosis through the balance of life). Data from a randomly selected sample of breast cancer survivors with (n=25) and without (n=25) chronic PIPN were used in this analysis.

Demographic and Clinical Designs

Survivors with PIPN had changes in sensation and/or pain in their feet and/or hands of >3 months duration following the completion of CTX; had a rating of >3 on a 0 to 10 numeric rating scale (NRS) for any one of the following sensations from the Pain Quality Assessment Scale (PQAS;81 i.e., numb, tender, shooting, sensitive, electrical, tingling radiating, throbbing, cramping, itchy, unpleasant); if they had pain associated with the CIPN, had an average pain intensity score in their feet and/or hands of >3 on a 0 to 10 NRS.

Survivors provided information on demographic characteristics and completed the Alcohol Use Disorders Identification Test, the Karnofsky Performance Status (KPS) scale, and the Self-Administered Comorbidity Questionnaire (SCQ).

Gene Expression Measurement

Total RNA was isolated from peripheral blood samples collected at the time of the assessment using PAXgene® Blood RNA tubes and treated to deplete cytoplasmic ribosomal RNA and human globin mRNA. 100bp PE reads were aligned to the GRCh38 assembly of the human genome and Gencode v24 primary assembly of the transcriptome using the STAR aligner.

Differential gene expression (DGE) was assessed with edgeR. Significant demographic and clinical characteristics and surrogate variables were included in the model. Pathway perturbations were evaluated using KEGG signaling pathways and a cutoff-free pathway impact analysis with Pathway Express.¹ Whole-transcriptome DGE profiles of similar experiments were identified using ProfileChaser.

Results

Differences in Demographic and Clinical Characteristics

- BC survivors with PIPN were significantly older; more likely to be unemployed; reported lower alcohol use; had a higher BMI, and poorer functional status; and had a higher number of lower extremity sites with loss of light touch, cold, and pain sensations, and higher vibration thresholds.
- No between group differences were found in the total dose of paclitaxel received or in the percentage

Results (Continued)

Neuroinflammation Related Signaling Pathways

- Of the 52 significantly perturbed KEGG signaling pathways (FDR <.01), 8 were related to inflammatory processes.
- Of the 280 profiles across 84 unique GEO Datasets (GDS), 27 from 15 unique GDS were related to inflammatory processes.

Table 1. Significantly Perturbed Inflammation Related KEGG Signaling Pathways Between Breast Cancer Survivors With and Without PIPN.

ID	Name	Total Pert	pPert (FDR)
Hsa04060	Cytokine-cytokine receptor interaction	6.37	0.004
Hsa04064	NF-κβ signaling	4.50	0.005
Hsa04727	GABAergic synapse	4.63	0.007
Hsa04920	Adipocytokine signaling	9.13	0.008
Hsa04657	IL-17 signaling	3.15	0.010
Hsa04621	NOD-like receptor signaling	11.32	0.004
Hsa04152	AMPK signaling	15.14	0.004
Hsa04340	TGF-β signaling	10.30	0.010

Table 2. Experimental systems of inflammatory responses, exercise-induced effects, and pre-clinical models of pain with similar whole-transcriptome profiles to breast cancer survivors with PIPN vs. without PIPN.

GEO ID	Name	q-value	Tissue
GDS2439	28d vs 50d after L5 SNL	0.046	<i>R. norvegicus</i> DRG
GDS259	3d vs. 2d after SCI at T9	0.056	<i>R. norvegicus</i> SC
GDS2159	Moderate SCI vs. naïve	0.037	<i>M. musculus</i> SC
GDS1499	Control vs. HIV-1, drug naïve	0.045	<i>H. sapiens</i> PBMC
GDS1971	Complicated malaria vs. healthy	0.007	<i>H. sapiens</i> PBMC
GDS2310	After vs. before exhaustive exercise	0.003	<i>H. sapiens</i> WBC
GDS2417	Post- vs. pre-exercise	0.036	<i>H. sapiens</i> WBC

Discussion

Neuroinflammation and the development and maintenance of PIPN

The central and peripheral nervous systems are protected by the blood-brain barrier and blood-nerve barrier, respectively. However, small and large molecules and macrophages can cross the layers of satellite glial cells of the DRG. Chemokines and cytokines can mediate neuron-glia communication and nociceptive signal transmission. The subsequent recruitment of immune cells and neuroinflammation sensitize nociceptors and contributes to the development and maintenance of CIPN. Altered excitability of peripheral neurons may occur through the effect of increased inflammation at the site of injury.

Conclusions

To our knowledge, this is the first study to identify candidate genes and networks related to inflammation that were associated with PIPN, using peripheral blood samples from breast cancer survivors with and without this neurotoxicity. These findings identified genes and pathways for validation and as potential therapeutic targets.

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1. Kober et al. Expression of mitochondrial dysfunction-related genes and pathways in paclitaxel-induced peripheral neuropathy in breast cancer survivors. Mol Pain. 2018. PMID:30426838.