Gene expression profiling of evening fatigue differs by cancer diagnosis in oncology patients undergoing chemotherapy

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Introduction

Cancer-related fatigue (CRF) occurs in 14% to 96% of patients undergoing cancer treatment. CRF can lead to treatment discontinuation and current interventions for CRF are not efficacious. A critical barrier to the development of successful interventions is the lack of understanding of the mechanisms underlying CRF. [1] While some demographic, clinical, and genetic risk factors for CRF are known, the biological changes (i.e., gene expression) that result from the interactions among these risk factors are not well understood.

Investigation of molecular mechanisms associated with fatigue severity in oncology patients may identify new therapeutic targets. However, findings are inconclusive as to whether or not a patient's cancer diagnosis influences the phenotypic and molecular characteristics associated with fatigue severity.

While the majority of research on fatigue reported mean changes in fatigue severity, work from our research team and others suggests that the severity of fatigue varies over the course of a day and varies substantially among individuals. [3] Previous latent class analysis (LCA) identified three subgroups of oncology patients (n=582) with distinct evening fatigue trajectories over two cycles of CTX (i.e., Moderate (20.0%), High (21.8%), and Very High (58.2%)). [4] Patients who were younger, had a lower performance score, and a higher comorbidity score were more likely to be in the VH compared to the M fatigue class. Number of metastatic sites, CTX cycle length, and reason for current cancer treatment did not predict latent class membership.

The objective of this study was to compare differential gene expression (GE) between patients with Moderate and Very High levels of evening fatigue for the sample as a whole (W, n=257) and for patients with breast cancer (BC, n=103).

Materials and Methods

- Oncology outpatients (n=582) who were receiving CTX for breast, lung, gynecological, or gastrointestinal cancers were recruited as part of the parent grant (CA134900).
- Patients beginning their 2nd or 3rd cycle of CTX were assessed over 2 complete CTX treatment cycles (i.e., 6 assessments).
- Whole blood was collected at the time of the patient's enrollment into the study (i.e., immediately before their next dose of CTX).
- Gene expression was assayed for 281 patients using the Illumina Human HT-12 microarray.
- Differential expression (DE) were determined between groups (i.e., Moderate vs. Very High) for genes (limma) and pathways (GAGE, PathwayExpress). Batch effects were assessed for with SVA.
- BMI, KPS, Age, Microarray, Gender (W), and Cancer type (W) were included as co-variates in the linear models.

Results

Table 1. Differences in Demographic and Clinical Characteristics Between Lower and Higher Evening Fatigue

Significantly Different Demographic or Clinical Characteristics[a]	Moderate Fatigue (n=65) Mean (SD)	Very High Fatigue (n=195) Mean (SD)	p-value
Age (years)	60 ± 12	56 ± 12	t=2.39, p=0.018
Lee Fatigue Scale evening fatigue score	3.1 ± 1.5	6.4 ± 1.5	t=-15.81, p<0.000
Karnofsky Performance Status score	84.0 ± 11.2	77.9 ± 11.5	t=3.45, p=0.001
Gender (female)	45 (69.2)	166 (85.1)	FE, p=0.006
Prior cancer treatment [b]			X^2=11.67, p=0.009
None	15 (23.1)	23 (11.9)	
Only CTX, surgery, or RT	24 (36.9)	96 (49.7)	
CTX and surgery, or surgery and RT, or CTX and RT	19 (29.2)	34 (17.6)	
CTX, surgery, and RT	7 (10.8)	40 (20.7)	

[a] No significant difference was found between moderate and very high evening fatigue groups for the characteristics of: education, Self Administered Comorbidity Questionnaire score, time since diagnosis (years), hemoglobin, hemocrit, number of metastatic sites including lymph node involvement, number of metastatic sites excluding lymph node involvement, Self-reported ethnicity, married or partnered, lives alone, currently employed, annual household income, exercise on a regular basis, child care responsibilities, elder care responsibilities, AJCC Status, and metastatic sites in either W or BC samples.
[b] Post-hoc contrasts failed to reveal the subgroup(s) underlying the difference in prior cancer treatments observed in the Moderate as compared to the Very High Evening Fatigue group in either the W or BC samples.

Results

Table 2 – Top Differentially Expression Genes (DEG)[a] Between Moderate and Very High Evening Fatigue Groups

W	W ∩ BC [b,c]	BC
n=57	n=1 (7,165)	n=1670
e.g., UBD	i.e., GALR2	e.g., CCR10
IGSF10		IL19
MAPK14		IL17RC
OPRL1		BMF
ST5		EGFR

[a] DEG (Limma) were assessed at an FDR of 10% for BH-adjusted *p*-values; |Log Fold-Change| <1.0.; [b] Count of DEG (FDR10) in both W and BC;[c] (Count of DEG (FDR10) in W also putative DEG (p<0.05) in B, vice-versa).

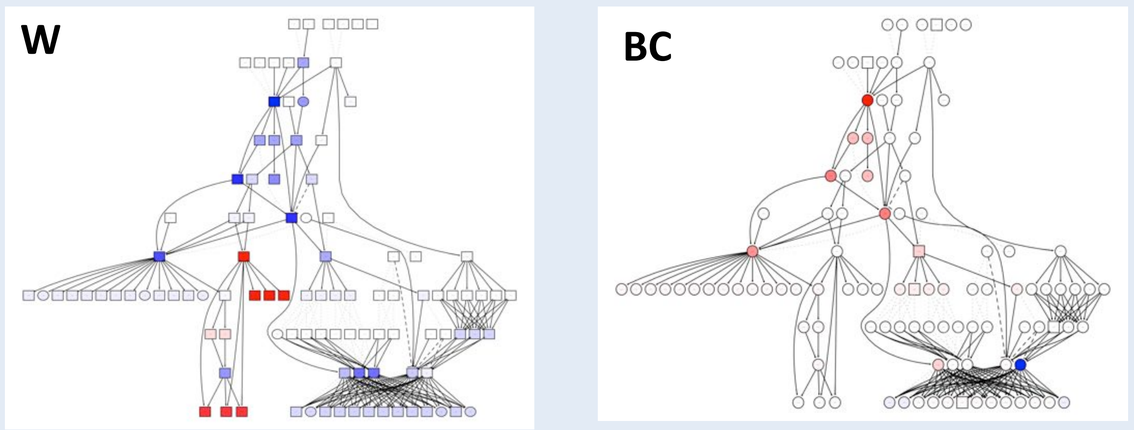
Table 3 – Top Differential Perturbed Pathways (DPP)[a] Between Moderate and Very High Evening Fatigue Groups

Direction	W	W ∩ BC [b,c]	BC
2D	n=164 e.g., Glycerolipid metabolism, Histidine metabolism	n=140 (155,160) e.g., Chemokine signaling pathway, Oxidative phosphorylation	n=164 e.g., Starch and sucrose metabolism, GnRH signaling pathway
Down	n=60 e.g., Glycolysis / Gluconeogenesis, Insulin signaling pathway	n=26 (44,27) e.g., Antigen processing and presentation, Protein export	n=38 e.g., Selenocompound metabolism, PPAR signaling pathway
Up	n=0 e.g., N/A	n=0 (0,1) i.e., N/A	n=9 e.g., Bacterial invasion of epithelial cells, Inositol phosphate metabolism

[a] DPP (GAGE) were assessed at an FDR of 20% for BH-adjusted *p*-values for 229 KEGG biological pathways. [b] Count of DPP (FDR20) in both W and BC;[c] (Count of DPP (FDR20) in W also putative DPP (p<0.05) in B, vice-versa).

Figure 1 – Accumulation of gene expression signal in the "NOD-like receptor signaling" pathway

A B



Differential perturbation of KEGG pathway hsa04621 using PathwayExpress. Combined significance of accumulation. The color of each node represents the perturbation (red = positive, blue = negative). The shade represents the strength of the perturbation. Square nodes with no parents have no accumulation

Conclusions

- Patients in the VH evening fatigue group were younger, had lower performance, and higher BMI in both W and BC samples.
- No differences were found between the two fatigue groups in hemocrit, hemoglobin, or exercise on a regular basis in both W and BC samples.
- One common and many distinct DEG were found between W and BC samples.
- Both common and distinct DPP were found between W and BC samples.
- Our results corroborate previous findings that GE differences in inflammation and immune response pathways are associated with evening CRF severity [1,5,6]
- Our results suggest that both common and distinct molecular mechanisms contribute to evening CRF
- Future studies should investigate other cancer diagnosis
- To better understand the relative contributions of genetic and epigenetic factors on gene expression, future studies should integrate methylation and genetic data.

References

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