Epigenetic Mechanisms of Inflammation and Fatigue in Patients with Cancer

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The National Comprehensive Cancer Network:

- A distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment not proportional to recent activity and interfering with usual functioning.
The most common side effect of cancer treatment

91% of fatigued patients: a disturbed normal life

75% of cancer patients: changed employment status as a result of fatigue

Decreasing adherence to treatment recommendations

Pre or post RT fatigue: prognostic of pathologic tumor response and survival
New Head and Neck Cancer Cases

- 2012: 40,250
- 2014: 55,070
- 2016: 61,760
High rates of fatigue during treatment (concurrent chemoradiotherapy)

Patients receiving intensity-modulated Radiation Therapy (IMRT): higher fatigue compared to conventional RT

An increase in baseline fatigue of 10 points (out of 100) yields a 17% reduction in survival
90%: fatigue
73%: ≥ moderate
Quality of Life as a Survival Predictor for Patients with Advanced Head and Neck Carcinoma Treated with Radiotherapy

BACKGROUND. Accumulating reports suggest that survival in patients with malignant cancer is related to fatigue at baseline and changes for patients with advanced head and neck carcinoma treated with radiotherapy.

![Graph showing overall survival for patients with fatigue scores below and above median (33.3) at baseline.]

FIGURE 1. Overall survival of patients with fatigue scores lower than the median (33.3) at baseline compared with patients with fatigue scores higher than the median.
High rates of fatigue during treatment (concurrent chemoradiotherapy)

Patients receiving intensity-modulated Radiation Therapy (IMRT): higher fatigue compared to conventional RT

An increase in baseline fatigue of 10 points (out of 100) yields a 17% reduction in survival
However, the management of fatigue is challenging.

There is no FDA-approved pharmacological agent that can reliably prevent or treat this symptom.
Cancer Treatment Stress

Hypothesis

Fatigue Depression

Pro-inflammatory Cytokines

Th1 INF-γ TNF-α IL-2 IL-6 IL-12
WHY YOUR DNA ISN'T YOUR DESTINY

The new science of epigenetics reveals how the choices you make can change your genes—and those of your kids

BY JOHN CLOUD
Epigenetics

- However, the mechanisms for the persistence of inflammation and fatigue long after treatment completion have yet to be understood.
- Epigenetics refers to the regulation of gene activities that does not involve alteration of DNA sequence.
- Environmental stimuli, such as diet, pollution, infections, or cancer treatment, have profound effects on epigenetic modifications that can, thereafter, trigger susceptibility to disease or symptoms.
DNA Methylation

Adds methyl (CH₃) groups to Cytosine base (C) when it is followed by a Guanine (G).
Target gene **expressed**

Target gene **silenced**

(Fry, 2011)
Inactivation of tumor suppressor genes such as p53

CpG hyper methylation

Normal Methylation

Global hypo methylation

Inactivation of DNA repair genes

Retrotransposon activation?  
Oncogene activation  
Chromosome instability
DNA methylation is the well-studied epigenetic modification, and has been characterized in various disease processes including cancer, psychiatric symptoms, and inflammation.

Our hypothesis is that cancer and its treatment leads to acute, but long-lasting epigenetic changes that may predispose to persistent inflammation and fatigue.
METHODOLOGY

Design: pre- to 1-year post-IMRT

Fatigue: Multidimensional Fatigue Inventory-20

Plasma IL-6, sTNFR2, CRP, NFkB activity, GR function, mRNA Gene expression, and DNA methylation

Covariates: age, gender, race, marital status, smoking, alcohol, BMI, cancer site, stage, treatment, RT does, other side effects.
Pilot data: 12 HNC patients

6 patients:
• ≥ 25 points increase from pre to post IMRT

6 patients:
• <15 point increase from pre to post IMRT
We evaluated DNA methylation changes across the genome before and after chemoIMRT.

- DNA methylation of CpG sites in 643 genes changed more than 10%.

We next evaluated whether methylation of CpG sites that changed before and after chemoIMRT associated with differences in fatigue.

- 306 chemoIMRT-responsive CpG sites (25.5%) associated with fatigue ($p<0.05$)
### CpG sites that were most associated with fatigue

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The association between fatigue and CpG sites in the IL-6 receptor gene
- **R01NR015783**  
  - Xiao (PI)  
  - 4/22/2016 – 3/31/2019  
  - Epigenetic Mechanisms of Inflammation and Fatigue in Head and Neck Cancer Patients  
  - **Role: PI**

- **K99/R00NR014587**  
  - Xiao (PI)  
  - 9/27/2013 – 6/30/2019  
  - Fatigue in Head and Neck Cancer: Role of pro- and anti-inflammatory signaling  
  - **Role: PI**
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