Underlying biological mechanisms and pathophysiology of cancer-related fatigue

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What causes fatigue?

Fatigue
Fatigue

Demographic factors

• Age
• Income
• Marital status
Fatigue

Demographic factors
• Age
• Income
• Marital status

Psychosocial factors
• Depression
• Catastrophizing coping style
Fatigue

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Health behaviors
- Physical activity
- Sleep disturbance
Fatigue

Comorbid symptoms
- Pain
- Menopausal sx

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Comorbid medical conditions
- Cardiovascular disease
- BMI

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Biological factors
- Anemia
- Inflammation

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Inflammation

• Body’s response to infection or injury
• Mediated by proinflammatory cytokines
  – IL-1β, IL-6, TNF-α
• Local and systemic effects, including effects on the brain
“Sickness behavior”

- Fatigue/ reduced activity
- Decreased food and water intake
- Decreased social and sexual behavior
- Alterations in cognition and mood
Model of cancer-related fatigue

Cancer and cancer treatment → Inflammation → FATIGUE
Inflammation and CRF

• Research conducted over past 10+ years has examined links between fatigue and inflammation in cancer populations
  – Studies have generally supported an association between fatigue and markers of inflammation
  – Negative results also reported
  – Range of patient populations and inflammatory markers assessed
Inflammation and pre-tx fatigue

• Ovarian cancer patients (Lutgendorf et al., 2008)
  – Fatigue and other vegetative symptoms of depression correlated with circulating levels of IL-6
  – In animal model, tumor-associated production of proinflammatory cytokines associated with reduced locomotor activity (Lamkin et al., 2011)

• Breast cancer patients (Fagundes et al., 2012)
  – CRP not elevated in women classified as “fatigued”
Inflammation and on-tx fatigue

- Radiation therapy
  - Early studies found mixed support for link between inflammatory markers and fatigue
  - Noisy system; variability within and across individuals may make it difficult to identify relationships
  - Results may depend on biomarker, timing of assessment, and analytic method
Inflammation and on-tx fatigue

• Chemotherapy
  – Breast cancer: sICAM linked to fatigue during chemotherapy (Mills et al., 2005)
  – Colorectal, esophageal, non-small cell lung cancer: inflammatory markers linked to fatigue during combined chemotherapy and radiation therapy (Wang et al., 2010, 2012)
Inflammation in cancer survivors

• Growing number of studies have examined links between inflammation and persistent, post-treatment fatigue
• Reasonably strong evidence for elevated inflammation in fatigued survivors
Elevated inflammatory markers in post-treatment fatigue

5 years post-treatment

Bower et al., 2002
Elevated inflammatory markers in post-treatment fatigue

5 years post-treatment

2.5 years post-treatment

Bower et al., 2002

Collado-Hidalgo, Bower et al., 2006
Fatigue correlated with inflammatory markers at one month post-treatment

A: No chemotherapy

B: Chemotherapy

Association significant controlling for age, BMI

Bower et al., JCO, 2011
Inflammation and post-tx fatigue

- Recent, larger studies focusing on survivors with severe, persistent fatigue confirm elevations in inflammatory biomarkers
  - Breast cancer survivors
    - Alexander et al., 2009 (n = 164)
    - Orre et al., 2011 (n = 299)
    - Alfano et al., 2012 (n = 633)
  - Testicular cancer survivors
    - Orre et al., 2009 (n = 283)
- Mixed results from smaller studies with more heterogeneous samples of patients
Model of cancer-related fatigue

Cancer and cancer treatment → Inflammation → FATIGUE
Individual differences in fatigue

• There is considerable variability in fatigue symptoms
  – Only a subgroup experience severe, persistent fatigue
Low and high fatigue groups after breast cancer treatment

Donovan et al., Health Psych, 2007
Risk factors for fatigue

- What puts some patients at risk for cancer-related fatigue?
- Focus on host factors associated with increased inflammatory activity
  - Genetic
  - Neuroendocrine and immune
  - Biobehavioral
Model of cancer-related fatigue

Cancer and cancer treatment → Inflammation → FATIGUE
FATIGUE

Cancer and cancer treatment

Genetic factors
SNPs in cytokine genes

Biobehavioral factors
Stress, depression, sleep, BMI

Neuroendocrine system
HPA axis
ANS

Immune system
Viral reactivation

Inflammation

FATIGUE
FATIGUE

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FATIGUE
HPA regulation of inflammation

- Alterations in cortisol production/release
- Alterations in glucocorticoid receptor signaling

Elevated evening cortisol in fatigued BCS

Salivary cortisol (log ng/dL)

- O - Fatigued BCS
- - Non-fatigued BCS

Hour of sample collection

Bower et al., Psychoneuroendocrinology, 2005

B = 0.092, p < .018
Blunted cortisol response to stress in fatigued BCS

Group x Time interaction: $F = 4.5$, $p = .001$

Bower et al., *Psychosom Med*, 2005
Cortisol production and fatigue

- Ovarian cancer patients before surgery
  - Fatigue linked to higher evening cortisol, reduced cortisol variability (Weinrib et al., 2010)

- Melanoma patients before IFN therapy
  - Exaggerated HPA response to initial treatment predicted development of depressive symptoms (Capuron et al., 2003)
Alterations in glucocorticoid receptor sensitivity in fatigued survivors

• Under-expression of genes bearing anti-inflammatory glucocorticoid response elements

Bower et al., 2011
Alterations in glucocorticoid receptor sensitivity in fatigued survivors

- Under-expression of genes bearing anti-inflammatory glucocorticoid response elements
- Over-expression of genes bearing response elements for pro-inflammatory NF-κB

Bower et al., 2011
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FATIGUE
Genetic risk factors and fatigue

• During treatment
  – SNPs in *TNFA* and *IL6* associated with fatigue during RT for breast, prostate, lung, or brain cancer (Aouizerat et al 2009, Miaskowski et al 2010)
  – SNPs in *TNFA* and *IL6* associated with fatigue during androgen deprivation therapy for prostate cancer (Jim et al., 2012)

• Post treatment
  – SNPs in *IL1B* and *IL1RN* associated with fatigue in large sample of lung cancer survivors (Rausch et al 2010)
Implications for treatment

- If inflammation is driving fatigue, interventions that target inflammation may be effective in reducing CRF
  - Pharmacologic interventions?
  - Exercise?
  - Stress management?
  - Mind-body therapies? (e.g., yoga, Tai Chi, Qigong)
Future directions

• Animal models of cancer-related fatigue to probe underlying mechanisms
• Prospective, longitudinal studies that comprehensively evaluate predictors and associated mechanisms
• Focus on downstream biomarkers of inflammatory cytokine activity
  • CRP, soluble TNF receptors, etc.
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