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Sestrin Family of Genes and their role in Cancer-related Fatigue

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Cancer-related fatigue (CRF) continues to be a prevalent and distressing symptom experienced by cancer patients and survivors. CRF is defined by the National Comprehensive Cancer Network as a “distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment, that is not proportional to recent activity and that interferes with usual functioning[1].” Although there is currently no optimal management and scant molecular evidence to guide the development of effective CRF therapies, several pathophysiological mechanisms have been proposed to explain the development of CRF[2–3]. These pathophysiological mechanisms of CRF are believed to be complex and involves a cascade of events including the dysregulation of several physiological and biochemical systems, such as oxidative stress, inflammation, immune modulation, circadian rhythms modulation, growth factors, serotonin dysregulation, hypothalamic-pituitary-adrenal-axis disruption, vagal-afferent-activation, and hematopoietic dysfunction[2–4]. Although these proposed mechanisms of CRF pathophysiology are yet to be independently investigated, recent evidence suggest a critical role of mitochondrial dysfunction/oxidative stress in CRF[4–5].

Association of Oxidative Stress with Cancer and CRF

Cancer and CRF have both been associated with oxidative stress and genomic instability [4–6]. The prominent feature of cancer cells is their metabolic transformation, which is their reckless acquisition of energy[7]. Briefly, this metabolic transformation in cancer cells demands a rapid supply of adenosine triphosphate (ATP) through the unquenchable consumption of glucose, depleting the mitochondria with available oxygen, and resulting in the overproduction of mitochondrial reactive oxygen species (ROS) triggering the excessive accumulation of mitochondrial-driven oxidative stress[7–8]. In addition, extrinsic factors

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Conflict of Interest

The authors have no conflict of interest to declare. All funding sources supporting this work are acknowledged in the acknowledgement section. The first author (VG) has full access and control to all the data in the study and accepts full responsibility for the integrity of the data and the accuracy of the data analysis. We allow the journal to review the data, if requested. All authors have made substantial contributions to this study and has seen and approved the final version of the manuscript.

such as radiation therapy and chemotherapy could contribute to the accumulation of oxidative stress [9]. Accumulation of oxidative stress is the reflection of the inability of the mitochondria to detoxify ROS [9]. Intracellular ROS can influence cellular processes such as cell growth [8,10]. The accumulation of ROS in the mitochondria has been linked as an apoptotic stimulus[10] and has been associated with CRF[11–12].

Dysfunctional mitochondria related to cancer and its treatment can impair the cell's ability to detoxify ROS, reactive nitrogen species (RNS), and other reactive metabolic intermediates[8,13], shifting mitochondrial respiration to a more glycolytic source, reducing the supply of ATP[3–4]. Reduced ATP supply deprives the cell of nutrients and energy which is believed to contribute to CRF development or intensification[3–5]. The link between reduced ATP supply and fatigue has been supported by prior exhaustive reviews[3–4].

The Sestrin Family of Genes

Understanding the role of genomics in cancer and in CRF is an expanding area of investigation. For example, concomitant over-expressions of the genes *ERα36*, *EGFR* and *HER2* were strongly associated with aggressive forms (e.g. lymph node metastasis and high staging) of papillary thyroid carcinoma[14].

Very limited studies have explored the use of genomic approaches to understand the pathobiology of CRF. *In vivo* studies have shown that differential expression of genes activating several physiological pathways, including those related to inflammation, neuroprotection, and mitochondrial dysfunction may contribute to the development and intensification of CRF[11–12,15]. Similarly, differential expressions of genes that regulate key mitochondrial functions (*AIFM2*, *IMMP2L*, *MSTO1*, *SLC25A23*, *SLC25A4*), the mitochondrial transport mechanism, and the respiratory chain (*BCS1L*, *SLC25A37*, *BCL2L1*, *FIS1*) were associated with fatigue in patients with non-metastatic prostate cancer receiving external beam radiation therapy (EBRT) [11–12]. This area of inquiry requires closer attention, so specific mitochondrial markers that can cause CRF can be identified. Further, there is no study that investigated markers of adaptive response to the excess of oxidative stress related to the metabolic demand of cancer and its treatment and their potential role in CRF development.

The Sestrin family of genes are stress-inducible metabolic regulators[16], and could be important markers to explore for their potential role in cancer and in CRF. In mammalian cells, Sestrin genes (*SESNI*, *SESN2*, and *SESN3*) are part of a family of genes that encode stress-responsive proteins[13, 17]. Compelling evidence suggest that Sestrins are involved in two central cellular functions, namely, the suppression of oxidative stress (reduction of ROS) and inhibitor of mechanistic target of rapamycin complex 1 (mTORC1) signaling in response to stresses[13,17]. Expressions of the Sestrin genes have been associated with effective adaptive cellular response to a variety of environmental stresses such as genotoxic stress/ deoxyribonucleic acid (DNA) damage, oxidative stress, and hypoxia; as well as in pathological conditions including cancer, hypernutrition, diabetes, obesity, and chronic fatigue syndrome[13,17]. For example, upregulation of *SESN2* was associated with longer

overall survival in individuals with non-small cell lung cancer [18]. *SESN2* has tumor suppression properties as was observed to be significantly downregulated in colon adenocarcinoma tissues compared to normal colon tissues [19]. There is also evidence that Sestrins could suppress different age-related pathologies given their capacity to increase the efficiency of the oxidative metabolism, mitochondrial biogenesis, and mTOR- regulating capabilities[13].

Further, Sestrins are thought to be activated, at least for *SESN1* and *SESN2*, by genotoxic stress in a p53-dependent manner. In fact, an earlier study provided support for *SESN2*-related DNA damage upon irradiation and genotoxic drug treatments on breast cancer cells through a poorly understood mechanism that may be related to the inhibition of mTORC1[20]. Other investigators have found that chemotherapy drugs trigger the expression of *SESN3* via Forkhead box (FOXO) transcriptional factors[10,17]. Nonetheless, inactivation of Sestrins can lead to oxidative damage and mitochondrial dysfunction[13]. *SESN1*, *SESN2*, and *SESN3* are linked to the metabolism of ROS and other reactive metabolites[13]. *SESN3* is specifically known for being involved in the maintenance of physiological concentrations of intracellular ROS[13]. In one study, it was observed that induction of *SESN3* by Forkhead box O3 caused a transitory decline in ROS production and delayed Forkhead box O3-induced apoptosis in neuronal cell lines[10]. Similarly, Kopnin et al.[21] found that down-regulation of *SESN3* in human Li-Fraumeni fibroblast cell line (MDAH041) caused increased ROS levels and chromosomal instability in cells expressing oncogenic RAS. Dysregulation of intracellular ROS homeostasis has been found to play a role in the development of many diseases, such as cancer, rheumatoid arthritis, and diabetes[17].

Conversely, it has also been suggested that Sestrins retained some antioxidant capabilities (preventing the accumulation of ROS within the cell)[13]; thus, potentially preventing CRF development or intensification. Parmigiani and Budanov[17] investigated the signaling pathways in which Sestrins exhibit their antioxidant functions. Among these is the regeneration of over-oxidized peroxidoxins, which direct ROS scavenging, attenuation of mTORC1-derived ROS, and inhibition of Nox4 expression. More specifically, it has been suggested that *SESN2* has the capability of stimulating the autophagic degradation of Kelch-like ECH-associated protein 1 (Keap 1), and in this manner upregulates the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, leading to the induction of antioxidant genes, such as the *SRX* gene[22]. In contrast, one study found evidence that overexpression of *SESN2* in HeLa or A549 cells did not affect the reduction of cysteine sulfinic acid of peroxiredoxins, thus suggesting no antioxidant function [23]. The potential Sestrins' roles in the antioxidant defense system have some clinical implications. In the future, antioxidant-based therapeutic or prophylactic strategies (e.g. exercise, antioxidant dietary supplementation) targeting activation or induction of Sestrin genes may be a reasonable approach for exploring how to reduce/inhibit CRF or even prevent cancer recurrence. It is also possible that this new knowledge may lead to a predictive candidate marker tool to identify patients at risk to develop debilitating toxicities of cancer therapies, including fatigue.

Sestrins and Behavior

Emerging data from genome-wide studies using microarray technology and other molecular approaches identify the Sestrin genes as being involved in behavioral symptoms including cognitive impairment, pain, and fatigue. Rai et al.[24] showed that the serum SESN2 protein concentration was significantly elevated in individuals with mild cognitive impairment as assessed by the Montreal Cognitive Assessment scores, as well as in patients with Alzheimer's Disease. Kallenborn-Gerhardt et al.[25] also observed that *SESN2* knockout mice displayed increased late-phase pain behavior (neuropathic); however, induced acute pain and inflammatory pain were unaffected. Further, *SESN1*, has been found to be a potential fatigue-relevant gene. Broderick et al.[26] used classical multivariate statistical methods to reduce data complexity, but retained biological information that had potential importance to understand the biologic underpinnings of the fatigue experience of individuals with chronic fatigue syndrome. That study found that *SENS1* was the most influential gene that was significantly correlated with fatigue symptoms of individuals with chronic fatigue syndrome[26].

Using microarray technology, we recently conducted a genome-wide study that identified transcriptional changes during EBRT from whole blood ribonucleic acid (RNA) of 26 Hispanic Puerto Rican men with non-metastatic prostate cancer [27]. We observed that *SESN3* (adjusted $p < 0.01$, log fold change -0.649) was significantly downregulated during EBRT, whereas the expressions of *SESN1* and *SESN2* remained unchanged. After adjustment for radiation fraction, differential expressions of two probes of *SESN3* (235684_s_at and 235683_at; again, after false discovery rate ([FDR] correction [FDR < 0.01]) were significantly associated with changes in fatigue (Functional Assessment of Cancer Therapy - Fatigue score) during EBRT.

In summary, the full spectrum of the role of Sestrins in CRF development and the signaling pathways involved are not yet known. Pilot studies are underway to confirm if Sestrin genes might be related to fatigue development or intensification, like the fatigue symptoms experienced by men receiving EBRT for non-metastatic prostate cancer. Mechanistic studies to further identify and comprehend physiologically relevant pathways can help us understand about the biological underpinnings of CRF. Notably, more research is needed to characterize the expression of this novel family of genes and to determine their role in the development of cancer-related behavioral symptoms including CRF.

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