Fundamental Mechanisms Underlying the Ill Health and Chronic Fatigue Syndrome Suffered by Atomic and Gulf War Veterans: A Unifying Hypothesis

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Introduction

These are two key hypotheses we wish to propose which will be discussed below.

1. CFIDS is caused by low dose chronic or acute exposure to stressors including radiation. The stress signalling leads to epigenetically sustained genomic instability in stem cell microenvironments producing the various immune, neurological and gastrointestinal symptoms.
2. Alleviation of CFIDS will involve understanding the initial signalling process and deactivating it or resetting it using inhibitors or epigenetic modifiers.

Background

CFIDS is a debilitating illness of unknown aetiology. It often manifests suddenly after exposure to stress or a flu-like illness (Katz and Jason 2013; Glaser and Kiecolt-Glaser 1998; Morris and Maes 2013; Bansal et al. 2012). However the symptoms which include multiple manifestations of both neurological, gastrointestinal and immune dysfunction (Maes et al. 2009; Maes and Twisk 2009; Moss-Morris et al. 2013), strongly suggest an underlying malfunction in the ability of the cells and tissues to manage cellular stress (Nicolson 2007; Hanley and Van de Kar 2003). We suggest that stem cells are a particular target and that regarding

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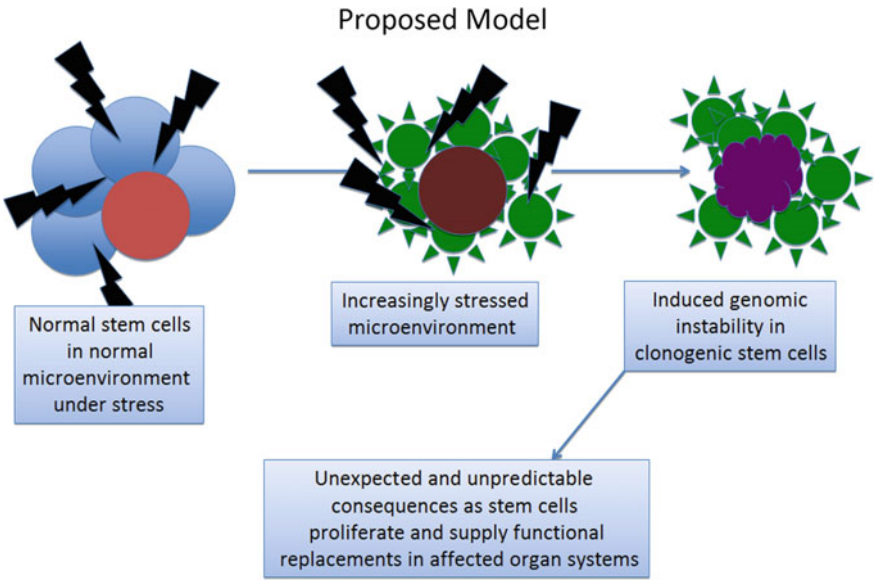

Fig. 1 Proposed model

CFIDS as a malaise of the stem cells might provide new insights into potential treatments (see Fig. 1 for the model).

Similar syndromes to CFIDS include the complex set of symptoms seen in Atomic Veterans and Gulf War survivors which are often dismissed as psychological (Ferguson and Cassaday 2001–2002; Israeli 2012; Garcia 1994; Murphy et al. 1990) because the small numbers and varied symptoms are not amenable to epidemiological analysis (McCauley et al. 2002; Coughlin 2013). However the variability in symptoms would imply that the abnormality may be unexpressed until a major stress event challenges the tissues to regenerate or otherwise become activated. The stress event could be biological e.g. viral infection, vaccine challenge, radiation or toxin exposure, or psychological e.g. war, catastrophic accidental event occurs which triggers the emergence of the full-blown syndrome (Maloney et al. 2013; Glaser et al. 1998; Witthöft et al. 2013). There is convincing but largely anecdotal evidence that chronic exposure to low doses of ionizing radiation (LDIR) is associated with neurological effects such as memory impairment, chronic fatigue syndrome and cognitive decline in humans (Marazziti et al. 2012; Ballesteros-Zebadúa et al. 2012; Huang 2012). The Cold War veterans represent the best example of this (Hansen and Schriner 2005) but because the prevailing theory in radiation biology and radiation protection did not recognise these low dose effects, the cohorts have not been well studied and are now too old to be systematically studied.

Major advances have now been made in our understanding of low dose effects in the laboratory and it is clear that these studies could significantly advance our

understanding of chronic ill health syndromes in general and CFIDS in particular. Recent evidence mainly funded by NASA, who are concerned about long term exposure to space radiation on cognitive function, fatigue and other non-cancer effects in astronauts (Cucinotta et al. 2013; Ushakov et al. 2011) implicates the neural stem cells in the process since these are extremely sensitive to LDIR (Kim et al. 2013; Etienne et al. 2012). The immune dysfunction symptoms could result from compromise of the bone marrow stem cells for which there is ample evidence linking radiation exposure to genomic instability in the stem cells (Mothersill and Seymour 2012; Szumiel 2014). Similarly gastrointestinal stem cells are also known to be extremely sensitive to low doses of radiation (Mothersill and Seymour 2012; Szumiel 2014). The mechanisms are unclear and obviously in order to treat or prevent the impacts of LDIR, mechanistic understanding of the process is crucial. This proposal aims to test the overall hypothesis that chronic fatigue and immune dysfunction syndrome (CFIDS) can become established in latent form as genomic instability maintained epigenetically though signalling (bystander effect) either due to genetic/epigenetic predisposition or as a result of chronic exposure to multiple stressors including LDIR. A trigger stress can then lead to full-blown expression of the disease.

Radiation biology has undergone a paradigm shift in recent years (for reviews see Mothersill and Seymour 2012; Szumiel 2014). The old idea was that DNA damage caused by radiation developed in a dose dependent manner and was usually efficiently repaired meaning that low doses caused very low or no effects (Hall 2011). Cancer was considered to be the only low dose effect and doses below 100 mGy were not considered to cause incidence above background (Morgan and Sowa 2013). Chronic doses and doses due to "internal emitters" i.e. ingested or inhaled radioisotopes were largely ignored (Mothersill and Seymour 2013). This all changed in the late 1980s and early 1990s when there were major breakthroughs which showed that the effects of ionizing radiation were very different after low doses and that even after high doses, repair was not an all-or-nothing affair. The phenomena of Lethal Mutations (Seymour et al. 1986), Genomic instability (Kadhim et al. 1992) and the Bystander Effect (Nagasawa and Little 1992) all suggested that effects of LDIR were very complex and very long lasting. Later research implicated the immune system (Hilgers and Frank 1994; Ojo-Amaize et al. 1994; Yancey and Thomas 2012; Lorusso et al. 2009) and linked cellular oxidative stress and inflammatory response to the perpetuation of a chronic dysfunction in affected cells, which could be inherited via epigenetic mechanisms (Landmark-Høyvik et al. 2010; Smith et al. 2008). Now it is accepted that these mechanisms are fundamentally important to the understanding of cellular and organismal responses to LDIR and many other stressors such as metals, organic toxins and pathological agents. Many mechanisms, particularly those involved in the initiation of the signalling pathways are still largely unknown although recent evidence from our laboratory implicates LDIR induction of UVA photons in exposed biological material and cells (Ahmad et al 2013; Le et al. in press). The UVA is thought to generate reactive oxygen species (ROS), which have long been known to compromise mitochondrial function and disrupt the sensitive control of inter and intra

cellular signalling (Festjens et al. 2006; Formigari et al. 2013; Frank et al. 2012; Morris and Maes 2014; Meeus et al. 2013; Volobouéva and Giffard 2011).

The theme, which comes through much of the literature about CFIDS is that it appears to have no one cause or clear set of symptoms. Its appearance can appear random and may be distant in time from an alleged triggering stress event. This is why its existence is sometimes denied by Western Medicine. However, this is exactly what would be predicted to happen if LDIR or other low dose toxic exposures were involved. It is particularly true if there is a two-stage etiological mechanism involving chronic low dose multiple stressor exposure followed by (or possibly preceded by) an acute mental or physical stress. One idea we will pursue throughout this research program is that CFIDS would have no clear cause or set of symptoms if it were a system level disease consequential upon systems not communicating or interacting as they should. Symptoms and causes would then be system specific. Individual predisposition to sensitivity would then be a most important factor (hence our interest in the impacts of chronic stressors during developmental). This individual, underlying sensitivity would be exacerbated by acute stressor exposure acting on the same or an interacting system. The mode of action of the stressors would also be important e.g. whether they act locally or systemically and whether exposure is local or systemic. A major focus of our research and possibly the major key to understanding CFIDS mechanisms is to understand the role of signalling processes in converting initially localised responses into systemic responses via processes such as "bystander signalling". Currently our research is suggesting that physical signals including photons in the UV range and phonons (sound vibrations) are key early initiating events when cells or organisms are exposed to LDIR (Mothersill et al. 2012). These signals may not initially be recognised as related to the LDIR exposure but we have shown they result in oxidative stress leading to inflammatory responses, which are of course systemic and deleterious and may underlie CFIDS pathology.

The section which follows is built around three quite specific research questions which we think should be explored to identify possible metabolic pathways which could be manipulated to reset the systemic disorder which underlies CFIDS.

What Are the Basic Mechanisms Involved in the Communication of Stress Between Cells in Tissues?

We need to explore how the physical electromagnetic energy (EM) associated with low dose exposures to electromagnetic radiation, is transduced to lead to biological responses in affected human patients. We know that UVA is involved and intend to explore what molecules absorb the UV energy and what results from this absorption. We suspect that the perturbation of delicately balanced voltage gated ion channels is involved and there is direct evidence for both sodium (Na v 1.5) and calcium (5HT-3A) ion gated channels being involved in the mechanism. We know that the energy perturbation results in activation of H-Ras and MAPK stress response

pathways but that instead of apoptosis occurring (which would remove damaged cells), a process known as genomic instability results. This is a permanent increase (reset) in the tolerance of the stem cell population for mutations. It is driven by bystander signals and is an example of an epigenetic control mechanism which results in chronically compromised stem cells in an abnormal microenvironment.

It will be important to investigate how mitochondria in stem cells coordinate function and decide response after toxin challenge. Of particular interest here is the putative photoreceptor in the mitochondrial membrane thought to be part of complex IV. This links in with our laboratory's recent work on UVA emission by cells when exposed to ionizing radiation which was discussed earlier. We do not know if other stressors such as metals can cause UVA emissions. However the common mechanisms seen in metal, bacterial and radiation challenged tissues and organisms strongly suggest a common underlying stress response which could involve UVA leading to ROS generation and consequent mitochondrial activity.

This area of research could be progressed by using co-culture systems where acutely stressed cells can signal to chronically stressed or control cells. Endpoints to be measured include bystander signal production, calcium and sodium fluxes across membranes using patch clamping, mitochondrial numbers, location and function, expression of key stress response proteins and UVA emission. Now that we have the antibody to the sodium channel Na v 1.5, associated with the ciguatera toxin which also is affected by chronic LDIR exposure, we will have a direct link between bystander signalling and channel activation in clonogenic stem cells.

Treatment of CFIDS Will Involve Elimination of Stress Signal Production and Resetting of the Supportive Microenvironment Which Allows the Aberrant Cells to Thrive

Several lines of evidence implicate LDIR exposure to internal emitters such as polonium, strontium, caesium, uranium or radium in the production of chronic ill-health and chronic fatigue syndromes. Classic examples are the ill-health of atomic veterans who were exposed during the Cold War, Gulf War personnel and inhabitants of Gulf War or nuclear bomb test countries e.g. the Marshall Islanders. While Governments mostly deny a causal link between ultralow dose radiation exposure and chronic ill health, because of weak epidemiology, a perfectly logical explanation is that the exposures lead to genomic instability driven by oxidative stress in the extremely sensitive stem cell compartments in the body which causes chronic inflammatory processes to occur and injures the microenvironment leading to a "self-sustaining" disease prone state. These processes are known to underlie many of the chronic conditions including CFIDS from which these cohorts suffer.

An approach which might prove useful would be to culture stem cells from key tissues such as brain (hippocampus), gastrointestinal crypts and bone marrow in

compromised micro-environments of support cells, which has been conditioned by LDIR exposure to signal stress to neighbouring cells. The behaviour of the stem cells in these conditions could be monitored using the assays suggested in Section "What Are the Basic Mechanisms Involved in the Communication of Stress Between Cells in Tissues?". It would also be useful to test the effectiveness of interfering with UVA production, with ROS, with MAPK pathways and with p53 pathways to see if this will prevent damage to the stem cells. Finally, there are established treatments for CFIDS promoted by practitioners of alternative medicine with proven effectiveness in eliminating symptoms such as the terpene D-limonene or curcumin. It would be very important to see if these substances are effective at preventing genomic instability from occurring or being expressed in the stem cells. This would provide useful confirmation of the correctness of our hypotheses.

Probing the Neurodevelopmental Processes as Affected by LDIR or Trace Metals and Microtoxins Thought to Be Involved in the Aetiology of CFIDS

As discussed earlier we now have substantial evidence that neurotransmitters and their inhibitors and activators can modulate response to toxin or radiation challenge even in non-neural cells. This is logical given that embryonic stem cells are pluripotent. It stands to reason that all cells have the potential to develop or express receptors if induced by the correct stimuli. In the case of stem cells in differentiated tissues, this potential is very great if the epigenetic information forthcoming. These mechanisms, if fully understood could lead to development of new drugs for modulating metal or radiation effects in cells, thus providing hope for CFIDS patients.

Membranes in the body function as barriers maintaining differential concentrations of ions on either side of the membrane by creating and maintaining a potential difference or electrical gradient. Channels in the membranes regulate the passage of sodium, potassium, calcium and chloride ions. These are known as ion channels and the passage of ions through them is tightly regulated.

The specific case of voltage-gated ion channel (VGIC) manipulation in the nervous system is of particular interest to those interested in LDIR because both radioactive metal ions similar to sodium, potassium or calcium (e.g. strontium, caesium, radium) and non-particulate ionizing radiation (e.g. x or gamma rays) would, by exciting or ionizing the membrane, upset delicate VGIC balances. This could lead to complex or chaotic responses. Channelopathies are linked to at least 20 diseases now including CFIDS (Kass 2005; Waxman and Ptacek 2000; Chaudhuri et al. 2000). A particular focus of our research will be the 5HT type 3A channel with we already know to be involved in the calcium response to LDIR (Fazzari et al. 2012; Mothersill et al. 2010; Saroya et al. 2009; Poon et al. 2007; Mothersill et al. 1976) and the sodium channel Na v 1.5 which is involved in

internalising ionizing radiation (radioisotopes) and is known to be altered in CFIDS patients (Fulle et al. 2003; Beyder et al. 2010; Abriel 2010). We hypothesise that very low doses of ionizing radiation can cause excitation of cell membranes leading to aberrant ion fluxes and initiation of inappropriate signalling—a systemic consequence. We postulate that the cognitive defects in CFIDS patients may result from this leading to a hypersensitive state in chronically stressed individuals.

Because we think that CFIDS is related to early exposure to chronic stress during development followed by an acute triggering exposure during later life, we suggest that human embryonic stem cells should be used for these experiments. These can be induced to differentiate along neural, gastrointestinal or bone marrow stem cell pathways and development can be tracked using a number of specific markers for tissue specific development and differentiation (Curtis et al. 2014; Wu and Wang 2012). Agonists and specific inhibitors should interfere with the differentiation pathway and allow us to pinpoint metabolic pathways implicated in the development of CFIDS.

Conclusion

This paper presents a working hypothesis which seeks to provide an explanation for a distressing collection of symptoms associated with low dose radiation exposure which result in Atomic Veterans syndrome, Gulf War syndrome, Chronic Fatigue and Immune Deficiency Syndrome and Myalgic Encephalomyelitis. Also presented is a possible research approach to improving treatment for sufferers of these complex diseases.

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References

Abriel H (2010) Cardiac sodium channel Na v 1.5 and interacting proteins: physiology and pathophysiology. J Mol Cell Cardiol 48(1):2–11

Ahmad SB, McNeill FE, Byun SH, Prestwich WV, Mothersill C, Seymour C, Armstrong A, Fernandez C (2013) Ultra-violet light emission from HPV-G cells irradiated with low let radiation from (90)Y; consequences for radiation induced bystander effects. Dose Response 11:498–516

Ballesteros-Zebadúa P, Chavarria A, Celis MA, Paz C, Franco-Pérez J (2012) Radiation-induced neuroinflammation and radiation somnolence syndrome. CNS Neurol Disord: Drug Targets 11 (7):937–949

Bansal AS, Bradley AS, Bishop KN, Kiani-Alikhan S, Ford B (2012) Chronic fatigue syndrome, the immune system and viral infection. Brain Behav Immun 26(1):24–31

Beyder A, Rae JL, Bernard C, Strege PR, Sachs F, Farrugia G (2010) Mechanosensitivity of Nav1.5, a voltage-sensitive sodium channel. J Physiol 588(Pt 24):4969–4985

Chaudhuri A, Watson WS, Pearn J, Behan PO (2000) The symptoms of chronic fatigue syndrome are related to abnormal ion channel function. Med Hypotheses 54(1):59–63

Coughlin SS, McNeil RB, Provenzale DT, Dursa EK, Thomas CM (2013) Method issues in epidemiological studies of medically unexplained symptom-based conditions in veterans. J Mil Veterans Health 21(2):4–10

Cucinotta FA, Kim MH, Chappell LJ, Huff JL (2013) How safe is safe enough? Radiation risk for a human mission to Mars. PLoS One 8(10):e74988

Curtis DJ, Sood A, Phillips TJ, Leinster VH, Nishiguchi A, Coyle C, Lacharme-Lora L, Beaumont O, Kemp H, Goodall R, Cornes L, Giugliano M, Barone RA, Matsusaki M, Akashi M, Tanaka HY, Kano M, McGarvey J, Halemani ND, Simon K, Keehan R, Ind W, Masters T, Grant S, Athwal S, Collett G, Tannetta D, Sargent IL, Scull-Brown E, Liu X, Aquilina K, Cohen N, Lane JD, Thoresen M, Hanley J, Randall A, Case CP (2014) Secretions from placenta, after hypoxia/reoxygenation, can damage developing neurones of brain under experimental conditions. Exp Neurol pii: S0014–4886(14)00137-X. doi:10.1016/j.expneurol.2014.05.003 (Epub ahead of print)

Etienne O, Roque T, Haton C, Boussin FD (2012) Variation of radiation-sensitivity of neural stem and progenitor cell populations within the developing mouse brain. Int J Radiat Biol 88 (10):694–702

Fazzari J, Mersov A, Smith R, Seymour C, Mothersill C (2012) Effect of 5-hydroxytryptamine (serotonin) receptor inhibitors on the radiation-induced bystander effect. Int J Radiat Biol 88 (10):786–790

Ferguson E, Cassaday HJ (2001–2002) Theoretical accounts of gulf war syndrome: from environmental toxins to psychoneuroimmunology and neurodegeneration. Behav Neurol 13(3–4):133–147

Festjens N, Vanden Berghe T, Vandenabeele P (2006) Necrosis, a well-orchestrated form of cell demise: signalling cascades, important mediators and concomitant immune response. Biochim Biophys Acta 1757(9–10):1371–1387

Formigari A, Gregianin E, Irato P (2013) The effect of zinc and the role of p53 in copper-induced cellular stress responses. J Appl Toxicol 33(7):527–536

Frank M, Duvezin-Caubet S, Koob S, Occhipinti A, Jagasia R, Petcherski A, Ruonala MO, Priault M, Salin B, Reichert AS (2012) Mitophagy is triggered by mild oxidative stress in a mitochondrial fission dependent manner. Biochimica et Biophys Acta (BBA)—Mol Cell Res 1823(12):2297–2310

Fulle S, Belia S, Vecchiet J, Morabito C, Vecchiet L, Fanò G (2003) Modification of the functional capacity of sarcoplasmic reticulum membranes in patients suffering from chronic fatigue syndrome. Neuromuscul Disord 13(6):479–484

Garcia B (1994) Social-psychological dilemmas and coping of atomic veterans. Am J Orthopsychiatry 64(4):651–655

Glaser R, Kiecolt-Glaser JK (1998) Stress-associated immune modulation: relevance to viral infections and chronic fatigue syndrome. Am J Med 105(3A):35S–42S

Hall EJ (2011) Radiobiology for the radiologist, 7th edn.

Hanley NR, Van de Kar LD (2003) Serotonin and the neuroendocrine regulation of the hypothalamic–pituitary-adrenal axis in health and disease. Vitam Horm 66:189–255

Hansen D, Schriner C (2005) Unanswered questions: the legacy of atomic veterans. Health Phys 89(2):155–163

Hilgers A, Frank J (1994) Chronic fatigue syndrome: immune dysfunction, role of pathogens and toxic agents and neurological and cardial changes. Wien Med Wochenschr 144(16):399–406

Huang TT (2012) Redox balance- and radiation-mediated alteration in hippocampal neurogenesis. Free Radic Res 46(8):951–958

Israeli E (2012) Gulf war syndrome as a part of the autoimmune (autoinflammatory) syndrome induced by adjuvant (ASIA). Lupus 21(2):190–194

Kadhim MA, Macdonald DA, Goodhead DT, Lorimore SA, Marsden SJ, Wright EG (1992) Transmission of chromosomal instability after plutonium alpha-particle irradiation. Nature 355 (6362):738–740

Kass RS (2005) The channelopathies: novel insights into molecular and genetic mechanisms of human disease. J Clin Invest 115(8):1986–1989
Katz BZ, Jason LA (2013) Chronic fatigue syndrome following infections in adolescents. Curr Opin Pediatr 25(1):95–102
Kim JS, Yang M, Kim SH, Shin T, Moon C (2013) Neurobiological toxicity of radiation in hippocampal cells. Histol Histopathol 28(3):301–310
Landmark-Høyvik H, Reinertsen KV, Loge JH, Kristensen VN, Dumeaux V, Fosså SD, Børresen-Dale AL, Edvardsen H (2010) The genetics and epigenetics of fatigue. PM R 2 (5):456–465
Le M, McNeill F, Seymour C, Rainbow A, Mothersill C An observed effect of ultraviolet-A radiation emitted from β-irradiated HaCaT cells upon non-β-irradiated bystander cells. Rad Res (in press)
Lorusso L, Mikhaylova S, Capelli E, Ferrari D, Ngonga GK, Ricevuti G (2009) Immunological aspects of chronic fatigue syndrome. Autoimmun Rev 8(4):287–291
Maes M, Twisk FN (2009) Why myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) may kill you: disorders in the inflammatory and oxidative and nitrosative stress (IO&NS) pathways may explain cardiovascular disorders in ME/CFS. Neuro Endocrinol Lett 30(6): 677–693
Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E (2009) Coenzyme Q10 deficiency in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is related to fatigue, autonomic and neurocognitive symptoms and is another risk factor explaining the early mortality in ME/CFS due to cardiovascular disorder. Neuro Endocrinol Lett 30(4):470–476
Maloney CD, Jensen S, Gil-Rivas V, Goolkasian P (2013) Latent viral immune inflammatory response model for chronic multisymptom illness. Med Hypotheses 80(3):220–229
Marazziti D, Baroni S, Catena-Dell'Osso M, Schiavi E, Ceresoli D, Conversano C, Dell'Osso L, Picano E (2012) Cognitive, psychological and psychiatric effects of ionizing radiation exposure. Curr Med Chem 19(12):1864–1869
McCauley LA, Joos SK, Barkhuizen A, Shuell T, Tyree WA, Bourdette DN (2002) Chronic fatigue in a population-based study of gulf war veterans. Arch Environ Health 57(4):340–348
Meeus M, Nijs J, Hermans L, Goubert D, Calders P (2013) The role of mitochondrial dysfunctions due to oxidative and nitrosative stress in the chronic pain or chronic fatigue syndromes and fibromyalgia patients: peripheral and central mechanisms as therapeutic targets? Expert Opin Ther Targets 17(9):1081–1089
Morgan WF, Sowa MB (2013) Non-targeted effects induced by ionizing radiation: mechanisms and potential impact on radiation induced health effects. Cancer Lett pii: S0304-3835(13) 00662-9. doi: 10.1016/j.canlet.2013.09.009
Morris G, Maes M (2013) A neuro-immune model of myalgic encephalomyelitis/chronic fatigue syndrome. Metab Brain Dis 28(4):523–540
Morris G, Maes M (2014) Mitochondrial dysfunctions in myalgic encephalomyelitis/chronic fatigue syndrome explained by activated immuno-inflammatory, oxidative and nitrosative stress. Metabolic brain disease. Springer, Berlin
Moss-Morris R, Deary V, Castell B (2013) Chronic fatigue syndrome. Handb Clin Neurol 110:303–314
Mothersill C, Seymour C (2012) Changing paradigms in radiobiology. Mutat Res 750(2):85–95
Mothersill C, Seymour C (2013) Uncomfortable issues in radiation protection posed by low-dose radiobiology. Radiat Environ Biophys 52(3):293–298
Mothersill C, Heffron JJ, McLoughlin JV (1976) Inhibition of actomyosin ATPase by high concentrations of 5-hydroxytryptamine. Possible basis of lesion in 5HT-induced experimental myopathy. Enzyme 21(6):481–487
Mothersill C, Saroya R, Smith RW, Singh H, Seymour CB (2010) Serum serotonin levels determine the magnitude and type of bystander effects in medium transfer experiments. Radiat Res 174(1):119–123
Mothersill C, Smith RW, Fazzari J, McNeill F, Prestwich W, Seymour CB (2012) Evidence for a physical component to the radiation-induced bystander effect? Int J Radiat Biol 88(8):583–591

Murphy BC, Ellis P, Greenberg S (1990) Atomic veterans and their families: responses to radiation exposure. Am J Orthopsychiatry 60(3):418–427

Nagasawa H, Little JB (1992) Induction of sister chromatid exchanges by extremely low doses of alpha-particles. Cancer Res 52(22):6394–6396

Nicolson GL (2007) Metabolic syndrome and mitochondrial function: molecular replacement and antioxidant supplements to prevent membrane peroxidation and restore mitochondrial function. J Cell Biochem 100(6):1352–1369

Ojo-Amaize EA, Conley EJ, Peter JB (1994) Decreased natural killer cell activity is associated with severity of chronic fatigue immune dysfunction syndrome. Clin Infect Dis 18(Suppl 1): S157–S159

Poon RC, Agnihotri N, Seymour C, Mothersill C (2007) Bystander effects of ionizing radiation can be modulated by signaling amines. Environ Res 105(2):200–211

Saroya R, Smith R, Seymour C, Mothersill C (2009) Injection of resperpine into zebrafish, prevents fish to fish communication of radiation-induced bystander signals: confirmation in vivo of a role for serotonin in the mechanism. Dose Response 8(3):317–330

Seymour CB, Mothersill C, Alper T (1986) High yields of lethal mutations in somatic mammalian cells that survive ionizing radiation. Int J Radiat Biol Relat Stud Phys Chem Med 50(1): 167–179

Smith AK, Dimulescu I, Falkenberg VR, Narasimhan S, Heim C, Vernon SD, Rajeevan MS (2008) Genetic evaluation of the serotonergic system in chronic fatigue syndrome. Psychoneuroendocrinology 33(2):188–197

Szumiel I (2014) Ionising radiation-induced oxidative stress, epigenetic changes and genomic instability: the pivotal role of mitochondria. Int J Radiat Biol 17:1–55

Ushakov IB, Petrov VM, Shafirkin AV, Shtemberg AS (2011) Problems of ensuring human radiation safety during interplanetary flights. Radiats Biol Radioecol 51(5):595–610

Voloboueva LA, Giffard RG (2011) Inflammation, mitochondria, and the inhibition of adult neurogenesis. J Neurosci Res 89(12):1989–1995

Waxman SG, Ptacek LJ (2000) Chronic fatigue syndrome and channelopathies. Med Hypotheses 55(5):457

Witthöft M, Hiller W, Loch N, Jasper F (2013) The latent structure of medically unexplained symptoms and its relation to functional somatic syndromes. Int J Behav Med 20(2):172–183

Wu Q, Wang X (2012) Neuronal stem cells in the central nervous system and in human diseases. Protein Cell 3(4):262–270

Yancey JR, Thomas SM (2012) Chronic fatigue syndrome: diagnosis and treatment. Am Fam Physician 86(8):741–746