Biomarkers Tied to UVA Exposure and Melanoma

Subjects: Medicine, General & Internal

Contributor: Alan Cocchetto, Colin Seymour, Carmel Mothersill

Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) is considered to be a multidimensional illness whose etiology is unknown. However, reports from Chernobyl, as well as those from the United States, have revealed an association between radiation exposure and the development of CFIDS.

Keywords: CFIDS/ME/CFS ; ionizing radiation ; UVA ; reactive oxygen species

1. Introduction

1.1. Background to the Model

CFIDS is known by several names that include Myalgic Encephalomyelitis (ME) as well as Chronic Fatigue Syndrome (CFS) [1]. Previous reports from Chernobyl and the United States have associated radiation exposure with CFIDS [2][3][4][5][6][7][8]. One report had identified chromosomal damage in a CFIDS patient cohort that had previously been screened for the presence of urinary radionuclides [9][10].

In this new systems biology model for CFIDS, the overall hypothesis is that exposure to radionuclides, either via ingestion or inhalation, leads to the constant liberation of low-level electromagnetic radiation due to radioactive decay. This could be viewed as a pathological process that develops gradually as a result of constant and repeated exposure to low doses of radiation, where localized internal damage would accumulate over time. Such an accumulation would be dependent on rates of radionuclide decay as well as the body's ability to deal with such an exposure by depuration, damage repair, or other mechanisms [11][12].

1.2. Background to the Proposed Mechanism

Cell exposure to beta or gamma rays has been shown to generate UVA and blue light biophotons [13][14]. The emission of light from irradiated organic material has been documented since the 1930s [15]. More recently a group characterized the emissions using a single photon counter and showed that the emitted light is mostly in the UVA range and low wavelength blue light [16][17]. The light emission can be shown to increase with radiation dose, and the biological response varies depending on the p53 status of the cell line that is exposed to the biophotons [18]. Investigations of the mechanism revealed that photosensitizers enhanced the biological cell-killing effect of the photons while melanin suppressed it [17][19]. Further examination of the system suggested that mitochondrial function was implicated, and a study of the electron transport chain confirmed that the function of mitochondrial complex 1 was completely blocked in cells receiving photon signals from other cells exposed to ionizing radiation [20]. Taken together, this body of work proves that cells grown in media containing radioisotopes or exposed to external radiation emit biophotons. These biophotons are mainly in the UVA wavelength band, and they can trigger downstream stress-like responses in cells receiving the biophotons that were never exposed to ionizing radiation. The involvement of mitochondrial complex 1 in the mechanism strongly suggests that ATP depletion and the consequent elevation of reactive oxygen species (see below) are key components in compromising efficient cell function. The mechanism is considered to explain bystander signaling, which is a non-targeted effect where cells exposed to ionizing radiation signals in non-irradiated cells induce responses indistinguishable from those seen in directly irradiated cells [15].

2. Biomarkers

2.1. STAT1

The STAT1 protein is a critical cell protein for proper immune function and regulation. Without it, cells are unresponsive to interferons, thereby leaving the body defenseless against viral and bacterial infections. Previous research has shown that

a subpopulation of CFIDS patients who have a STAT1 deficiency exist [21][22]. This immunodeficiency may underlie the increased susceptibility to infections seen in many patients.

In a systems model, a biphasic pattern similar to that of STAT1 activity was observed as a function of the UVA radiation dose [23]. Low-dose UVA radiation was found to directly affect STAT1 phosphorylation. Thus, low-dose UVA radiation was found to activate STAT1, while higher-dose UVA radiation suppressed STAT1. Other research groups have found UV radiation to inhibit STAT1 [24][25]. Another group developed a novel radiation-biomarker discovery platform that represented the top 500 genes identified by linear regression analysis. This platform was then reduced to a 10-hub network that included STAT1 as a significant radiation target [26]. In addition, STAT1 was found to be strongly associated with overall survival in melanoma patients, where high STAT1 mRNA levels were associated with better survival outcomes [27].

2.2. NaV1.5

Ciguatoxins are a class of toxic polyether compounds found in fish whose consumption causes ciguatera poisoning [28]. Chronic ciguatera poisoning has been associated with CFIDS [29]. Ciguatoxins act on the neuronal voltage-dependent sodium (Na) channel NaV1.5 [30][31]. Dr. Yoshitsugi Hokama's monoclonal antibody for CTX (Mab-CTX) directly detects alterations to NaV1.5 [32] and this specific antibody was previously identified to react with CFIDS patient blood as reported in several studies [33][34].

NaV1.5 is an integral membrane protein involved in the initiation and conduction of action potentials. Alterations to NaV1.5 have been associated with a variety of arrhythmic disorders, including long QT, Brugada, and sick sinus syndromes, as well as progressive cardiac conduction defect and atrial standstill. Changes in the NaV1.5 expression level and/or sodium current density have been frequently noticed in acquired cardiac disorders such as heart failure.

In a systems model, UVA radiation was found to hamper the fast inactivation of cardiac NaV1.5 [35]. Furthermore, the authors suggest that UVA radiation modification of NaV1.5 provides valuable clues for ischemia/reperfusion injury in the heart and the central nervous system. In addition, NaV1.5 has been found to be expressed in human melanoma cells and has been associated with cancer invasiveness and metastasis [36][37].

2.3. ASPH

ASPH, or asparaginyl beta-hydroxylase, has been found to be increased in CFIDS patients [38]. ASPH is a transmembrane protein and a member of the alpha-ketoglutarate-dependent dioxygenase family [39]. In the last few decades, accumulating evidence has indicated that ASPH expression is upregulated in numerous types of human malignant cancer and is associated with poor survival and prognosis [40]. The ASPH protein aggregates on the surface of tumor cells. ASPH is highly expressed in cancers of the liver, pancreas, stomach, colon, breast, prostate, lung and brain. ASPH is necessary and sufficient to promote tumor cell migration, invasion, motility, and distant metastatic spread both in-vitro and in-vivo [41].

In a systems model, UVA radiation was found to significantly upregulate ASPH [42]. ASPH may prove to be a novel immunotherapy target for patients with melanoma [40].

2.4. NK Cell Cytotoxicity

NK cells, also known as natural killer cells, are a type of cytotoxic lymphocyte critical to the immune system. NK cells have the ability to recognize and kill cells in the absence of antibodies and the major histocompatibility complex, thereby allowing for a quicker immune reaction to stressed cells. NK cells and B-cell lineage differentiation derive from a common lymphomyeloid hematopoietic progenitor [43]. NK cell cytotoxicity has previously been shown to be altered in CFIDS patients, where it can impact the cell's functionality [44]. Various NK cell subsets have been previously evaluated to uncover their degree of radiation sensitivity [45]. This group identified a highly pronounced decrease in the CD3-CD8+CD56+ bright subset of NK cells after radiation exposure. Furthermore, this subpopulation was found to be the most radiosensitive one. Interestingly, three CFIDS patient studies have each identified a decrease in CD3-CD8+CD56+ bright NK cells in these patient cohorts [46][47][48].

In a systems model, previous studies have shown that NK cell activity is suppressed by UVA radiation, which results in the suppression of delayed hypersensitivity responses and thus impacts immunity [49][50]. Furthermore, circulating CD56 bright NK cells inversely correlates with the survival of melanoma patients [51].

2.5. RBC Morphology

Changes to red blood cell rheology or shape have been previously identified in CFIDS patients [52][53][54]. Patient samples were found to lack deformability, indicated by the presence of stomatocytes or other non-discocytic surface changes on red blood cells (RBCs). RBC deformability is important for proper tissue perfusion and oxygenation due to the impact on microcirculatory blood flow.

In a systems model, previous research has shown that RBC rheology mainly depends on the spectrin network, which can be altered by oxidation processes within the cell [55]. This group used atomic force microscopy to study the changes in the spectrin matrix and RBC morphology during oxidation processes caused by UV radiation exposure. The number of normal discocytic RBCs decreased from 98% to 12% while generating increased numbers of stomatocytes, echinocytes, and spherocytes. Thus, the spectrin network was damaged by UV radiation exposure thereby adversely affecting RBC rheology and many of its downstream effects.

2.6. IFI16

IFI16, also known as gamma-interferon-inducible protein 16, is a sensor for intracellular DNA and a mediator of interferon induction as well as an innate antiviral defense. It was found to be significantly upregulated in CFIDS patients [56][57]. In parallel with an increased frequency of plasmablasts in CFIDS patients with relatively short disease duration, the expression level of IFI16 was found to be negatively correlated with disease duration in this cohort. In addition, IFI16 expression showed a positive correlation with IGHV3-30–3 frequency in CFIDS patients.

In a systems model, one group demonstrated that IFI16, normally restricted to the nucleus, could be induced to appear in the cytoplasm under conditions of UV radiation-induced cell injury [58]. Furthermore, IFI16 has been shown to be a novel signature associated with overall survival and immune infiltration of skin cutaneous melanoma [59].

2.7. SLC25A15

In a large UK Biobank CFIDS study, SLC25A15 was identified as being statistically significant. SLC25A15 encodes the Ornithine Transporter type 1 protein that transports ornithine across the inner membrane of mitochondria to the mitochondrial matrix and plays a role in the urea cycle [60]. This group suggested that SLC25A15 could be a causal gene for altered CFIDS risk.

In a systems model, one group identified that the overexpression of SLC25A15 was involved in the proliferation of cutaneous melanoma, leading to a poor prognosis [61].

2.8. ECP

ECP, also known as eosinophilic cationic protein, is a basic secretion protein involved in the immune system response [62]. ECP levels are an indicator of eosinophil-specific activation and degranulation. ECP levels have been found to be significantly higher in CFIDS patients and are modulated by exercise challenge [63][64].

In a systems model, ECP levels appear to be a novel prognostic serum marker for the overall survival outcome of melanoma patients [65]. Here, ECP levels were found to be inversely correlated with survival.

2.9. Heat Stroke and Heat Dissipation

In CFIDS patients, increased temperature has been found in widely distributed regions of the brain [66]. This group reasoned that regional brain temperature has been used as a proxy for measuring neuroinflammation, with the observation that microglia activation can increase metabolic demands, potentially leading to excess heat. Interestingly, another research group had outlined the similarity in the pathophysiological mechanisms that apply to heat stroke and overlap with CFIDS [67]. According to this group, the endotoxemia pathway is increasingly considered the leading driver of severe organ damage and the main cause of death in people suffering from heat stroke.

More recently, it was reported that Transient Receptor Potential Melastatin 3 (TRPM3) activity was lost in CFIDS patients, and there was no significant difference in TRPM3 ion channel activity between CFIDS patients and post-COVID-19 patients [68]. Interestingly, TRPM3 functions as a sensor for noxious heat and underlies heat sensitivity in a subset of sensory neurons [69]. In fact, TRPM3-deficient mice exhibited clear deficits in their avoidance responses to noxious heat and in the development of inflammatory heat hyperalgesia. Heat stroke and heat dissipation, in the context of melanoma,

are both involved in thermoregulation. This is in line with transient receptor potential ion channels and their role in both thermoregulation and thermosensation [70].

In a systems model, heat plays an additional role in melanoma. One group utilized thermal conductivity measurements as a tool to detect the micro-invasion of melanoma [71]. In accordance with tumor progression, effective thermal conductivity was higher in invasive melanoma. Likewise, another research group had identified fever as a factor contributing to long-term survival in a patient with metastatic melanoma [72]. They presented the unique case of a female patient who had suffered from MM for more than 13 years. The patient had several episodes of fever that were not deliberately treated with medication. After each fever episode, the patient observed the disappearance of tumors, which was confirmed by medical examination. Interestingly, since her initial diagnosis, the patient has refused most of the proposed medical treatments. Most of her malignant tumors have either disappeared or stabilized without further growth.

2.10. Exosomes

Exosomes are small vesicles enclosed by a lipid membrane bilayer and secreted by most cells in the body. They have been shown by a group to be released in response to the UVA bystander signal [16]. The treatment of unirradiated cells with these exosomes alone triggers a radiation-induced bystander effect, thus neatly confirming that the UVA signal triggers exosome release and may be upstream of exosomes in the mechanism of the radiation-induced bystander effect (RIBE) [73]. MicroRNAs (miRNAs) are the most numerous cargo molecules in the exosome. Because numerous miRNAs have been identified to date in CFIDS patients, researchers have chosen to focus on one in particular because of its importance to this model. One group has reported an increase in miR-21 in both moderately ill as well as severely ill CFIDS patients' plasma and peripheral blood mononuclear cells (PBMCs) [74]. This result was confirmed in different patient cohorts. According to this group, miR-21 down-regulates the Sirt1/eNOS axis via TGF-beta and TNF-alpha pathways in endothelial cells as well as endothelial progenitor cells. However, another research group reported a significant reduction in the expression levels of miR-21 in both the NK and CD8 T-cells in CFIDS patients [75].

Among the key research findings that support a proposed systems model is that miR-21 has been identified as being intimately involved in RIBE. Significant upregulation of miR-21 was found by Xu [76] in both directly irradiated cells and bystander cells, which was confirmed by the expression of miR-21 precursor and its target genes. Additional research has generated a proposed RIBE model for exosome-mediated transfer of miR-21 [77]. Thus, in irradiated cells, the expression of miR-21 is upregulated, and as a response, miR-21 sorting to exosomes is motivated. The exosomes are secreted out from the irradiated cells, diffused into the extracellular medium, and taken up by non-irradiated cells. The miR-21 inside the exosomes is then released into bystander cells to induce bystander effects. Once the exosome cargo, including miR-21, was released into the cytoplasm of recipient or bystander cells, the increased miR-21 level regulated the relevant target gene expression and induced chromosome aberration and DNA damage. In addition, miR-21 has been found to play a key role in melanomagenesis and melanoma progression [78]. Lastly, miR-21 has been found in glomerular injury as well as glomerulosclerosis [79][80].

References

1. Bell, D.S. The Disease of a Thousand Names: CFIDS—CHRONIC Fatigue/Immune Dysfunction Syndrome; Pollard Publications: La Jolla, CA, USA, 1991.
2. Loganovsky, K. Chronic Fatigue Syndrome as a Characteristic Aftermath of Radioecological Catastrophe. Int. J. Psychophysiol. 2000, 35, 69.
3. Loganovsky, K.N. Chronic Fatigue Syndrome in the Chernobyl Accident Consequences Liquidators. Int. J. Radiat. Med. 2001, 3, 76.
4. Loganovsky, K. Do Low Doses of Ionizing Radiation Affect the Human Brain? Data Sci. J. 2009, 8, 13–35.
5. Tang, F.R.; Loganovsky, K. Low Dose or Low Dose Rate Ionizing Radiation-Induced Health Effect in the Human. J. Environ. Radioact. 2018, 192, 32–47.
6. Bazyka, D.; Loganovsky, K.; Ilyenko, I.; Volovyk, S.; Perchuk, I.; Pleskach, O.; Nechayev, S. Psychophysiological, Neuroimmune and Gene Expression Changes in Chronic Fatigue Syndrome after Low-Dose Radiation Exposure. Int. J. Psychophysiol. 2010, 77, 340.
7. Loganovsky, K.N. Vegetative-Vascular Dystonia and Osteoalgetic Syndrome or Chronic Fatigue Syndrome as a Characteristic After-Effect of Radioecological Disaster. J. Chronic Fatigue Syndr. 2000, 7, 3–16.

8. National CFIDS Foundation. National CFIDS Foundation (NCF) Announces Link between Chronic Fatigue Syndrome a nd Low Level Radiation Exposure; PR Newswire: Chicago, IL, USA, 2010.
9. National CFIDS Foundation. National CFIDS Foundation's Research Finds Chromosome Damage in Patients Diagnos ed with Chronic Fatigue Syndrome and Myalgic Encephalomyelitis; PR Newswire: Chicago, IL, USA, 2014.
10. Heng, H.H.Q.; Liu, G.; Stevens, J.B.; Abdallah, B.Y.; Horne, S.D.; Ye, K.J.; Bremer, S.W.; Chowdhury, S.K.; Ye, C.J. Kar yotype Heterogeneity and Unclassified Chromosomal Abnormalities. Cytogenet. Genome Res. 2013, 139, 144–157.
11. Boubriak, I.; Akimkina, T.; Polischuk, V.; Dmitriev, A.; Mccready, S.; Grodzinsky, D. Long term effects of chernobyl conta mination on dna repair function and plant resistance to biotic and abiotic stress factors. TSitologiia Genet. 2016, 50, 34 –59.
12. Yushkova, E. Genetic mechanisms of formation of radiation-induced instability of the genome and its transgenerational effects in the descendants of chronically irradiated individuals of Drosophila melanogaster. Radiat. Environ. Biophys. 20 20, 59, 221–236.
13. Ahmad, S.B.; McNeill, F.E.; Byun, S.H.; Prestwich, W.V.; Seymour, C.; Mothersill, C.E. Ion Beam Induced Luminescenc e; Relevance to Radiation Induced Bystander Effects. Nucl. Instrum. Methods Phys. Res. Sect. B Beam Interact. Mater. At. 2012, 288, 81–88.
14. Ahmad, S.B.; McNeill, F.E.; Byun, S.H.; Prestwich, W.V.; Mothersill, C.; Seymour, C.; Armstrong, A.; Fernandez, C. Ultr a-Violet Light Emission from HPV-G Cells Irradiated with Low Let Radiation From (90)Y; Consequences for Radiation In duced Bystander Effects. Dose Response 2013, 11, 498–516.
15. Mothersill, C.; Le, M.; Rusin, A.; Seymour, C. Biophotons in Radiobiology: Inhibitors, Communicators and Reactors. Ra diat. Prot. Dosim. 2019, 183, 136–141.
16. Le, M.; McNeill, F.E.; Seymour, C.; Rainbow, A.J.; Mothersill, C.E. An observed effect of ultraviolet radiation emitted fro m beta-irradiated HaCaT cells upon non-beta-irradiated bystander cells. Radiat. Res. 2015, 183, 279–290.
17. Le, M.; Mothersill, C.E.; Seymour, C.B.; Ahmad, S.B.; Armstrong, A.; Rainbow, A.J.; McNeill, F.E. Factors affecting ultra violet-A photon emission from β-irradiated human keratinocyte cells. Phys. Med. Biol. 2015, 60, 6371–6389.
18. Le, M.; Mothersill, C.E.; Seymour, C.B.; Rainbow, A.J.; McNeill, F.E. An Observed Effect of p53 Status on the Bystander Response to Radiation-Induced Cellular Photon Emission. Radiat. Res. 2017, 9187, 169–185.
19. Cohen, J.; Vo, N.T.K.; Chettle, D.R.; McNeill, F.E.; Seymour, C.B.; Mothersill, C.E. Quantifying Biophoton Emissions Fro m Human Cells Directly Exposed to Low-Dose Gamma Radiation. Dose Response 2020, 18, 1559325820926763.
20. Le, M.; McNeill, F.E.; Seymour, C.B.; Rusin, A.; Diamond, K.; Rainbow, A.J.; Murphy, J.; Mothersill, C.E. Modulation of o xidative phosphorylation (OXPHOS) by radiation- induced biophotons. Environ. Res. 2018, 163, 80–87.
21. Knox, K.K.; Carrigan, D.R. Potential Role of STAT1 in the Pathogenesis of Chronic Fatigue Syndrome; Institute for Viral Pathogenesis: Madison, WI, USA, 2003.
22. Knox, K.K.; Cocchetto, A.; Jordan, E.; Leech, D.; Carrigan, D.R. Deficiency in the Expression of STAT1 Protein in a Sub population of Patients with Chronic Fatigue Syndrome (CFS). In Proceedings of the Seventh International AACFS Conf erence on Chronic Fatigue Syndrome, Fibromyalgia and other Related Illnesses, Madison, WI, USA, 8–10 October 200 4.
23. Maziere, C.; Dantin, F.; Dubois, F.; Santus, R.; Maziere, J. Biphasic Effect of UVA Radiation on Stat1 Activity and Tyrosi ne Phosphorylation in Cultured Human Keratinocytes. Free Radic. Bio. Med. 2000, 28, 1430–1437.
24. Aragane, Y.; Kulms, D.; Luger, T.A.; Schwarz, T. Down-regulation of interferon gamma-activated STAT1 by UV light. Pro c. Natl. Acad. Sci. USA 1997, 94, 11490–11495.
25. Kwon, T.R.; Oh, C.T.; Choi, E.J.; Kim, S.R.; Jang, Y.J.; Ko, E.J.; Suh, D.; Yoo, K.H.; Kim, B.J. Ultraviolet light-emitting-di ode irradiation inhibits TNF-α and IFN-γ-induced expression of ICAM-1 and STAT1 phosphorylation in human keratinoc ytes. Lasers Surg. Med. 2015, 47, 824–832.
26. Eschrich, S.; Zhang, H.; Zhao, H.; Boulware, D.; Lee, J.H.; Bloom, G.; Torres-Roca, J.F. Systems biology modeling of th e radiation sensitivity network: A biomarker discovery platform. Int. J. Radiat. Oncol. Biol. Phys. 2009, 75, 497–505.
27. Huang, L.; Chen, J.; Zhao, Y.; Gu, L.; Shao, X.; Li, J.; Xu, Y.; Liu, Z.; Xu, Q. Key candidate genes of STAT1 and CXCL1 0 in melanoma identified by integrated bioinformatical analysis. IUBMB Life 2019, 71, 1634–1644.
28. Friedman, M.A.; Fernandez, M.; Backer, L.C.; Dickey, R.W.; Bernstein, J.; Schrank, K.; Kibler, S.; Wendy, S.; Gribble, M.O.; Bienfang, P.; et al. An Updated Review of Ciguatera Fish Poisoning: Clinical, Epidemiological, Environmental, an d Public Health Management. Mar. Drugs 2017, 15, 72.
29. Pearn, J.H. Chronic fatigue syndrome: Chronic ciguatera poisoning as a differential diagnosis. Med. J. Aust. 1997, 166, 309–310.

30. Lombet, A.; Bidard, J.N.; Lazdunski, M. Ciguatoxin and brevetoxins share a common receptor site on the neuronal volta ge-dependent Na+ channel. FEBS Lett. 1987, 219, 355–359.

31. Rook, M.B.; Evers, M.M.; Vos, M.A.; Bierhuizen, M.F.A. Biology of cardiac sodium channel Nav1. 5 expression. Cardiov asc. Res. 2012, 93, 12–23.

32. Hokama, Y.; John A Burns School of Medicine, University of Hawaii, Honolulu, HI, USA. Personal communication, 200 8.

33. Hokama, Y.; Uto, G.A.; Palafox, N.A.; Enlander, D.; Jordan, E.; Cocchetto, A. Chronic phase lipids in sera of chronic fati gue syndrome (CFS), chronic ciguatera fish poisoning (CCFP), hepatitis B, and cancer with antigenic epitope resemblin g ciguatoxin, as assessed with Mab-CTX. J. Clin. Lab. Anal. 2003, 17, 132–139.

34. Hokama, Y.; Empey-Campora, C.; Hara, C.; Higa, N.; Siu, N.; Lau, R.; Kuribayashi, T.; Yabusaki, K. Acute phase phosp holipids related to the cardiolipin of mitochondria in the sera of patients with chronic fatigue syndrome (CFS), chronic Ci guatera fish poisoning (CCFP), and other diseases attributed to chemicals, Gulf War, and marine toxins. J. Clin. Lab. A nal. 2008, 22, 99–105.

35. Wang, G.K.; Wang, S.Y. Modifications of human cardiac sodium channel gating by UVA light. J. Membr. Biol. 2002, 189, 153–165.

36. Xie, A.; Gallant, B.; Guo, H.; Gonzalez, A.; Clark, M.; Madigan, A.; Feng, F.; Chen, H.D.; Cui, Y.; Dudley, S.C., Jr.; et al. Functional cardiac Na + channels are expressed in human melanoma cells. Onco. Lett. 2018, 16, 1689–1695.

37. Djamgoz, M.B.A.; Fraser, S.P.; Brackenbury, W.J. In Vivo Evidence for Voltage-Gated Sodium Channel Expression in C arcinomas and Potentiation of Metastasis. Cancers 2019, 11, 1675.

38. Roelant, C.H.S.; DeMeirleir, K.L. Methods and means for diagnosing and and/or treating a fatiguing illness. World Pate nt WO2019012159, 16 July 2018.

39. Hou, G.; Xu, B.; Bi, Y.; Wu, C.; Ru, B.; Sun, B.; Bai, X. Recent advances in research on aspartate β-hydroxylase (ASP H) in pancreatic cancer: A brief update. Bosn. J. Basic Med. Sci. 2018, 18, 297–304.

40. Zheng, W.; Wang, X.; Hu, J.; Bai, B.; Zhu, H. Diverse molecular functions of aspartate β-hydroxylase in cancer (Revie w). Oncol. Rep. 2020, 44, 2364–2372.

41. Wands, J.R.; De La Monte, S.; Aihara, A.; Olsen, M.J.; Thomas, J.M. Inhibitors of beta-hydroxylase for treatment of can cer. U.S. Patent Application 20200361925, 2 June 2020.

42. Radrezza, S.; Carini, M.; Baron, G.; Aldini, G.; Negre-Salvayre, A.; D'Amat, A. Study of Carnosine's effect on nude mice skin to prevent UV-A damage. Free Radic. Biol. Med. 2021, 173, 97–103.

43. Miller, J.S.; McCullar, V.; Punzel, M.; Lemischka, I.R.; Moore, K.A. Single adult human CD34(+)/Lin-/CD38(-) progenitor s give rise to natural killer cells, B-lineage cells, dendritic cells, and myeloid cells. Blood 1999, 93, 96–106.

44. Brenu, E.W.; Hardcastle, S.L.; Atkinson, G.M.; van Driel, M.L.; Kreijkamp-Kaspers, S.; Ashton, K.J.; Staines, D.R.; Mars hall-Gradisnik, S.M. Natural killer cells in patients with severe chronic fatigue syndrome. Auto Immun. Highlights 2013, 4, 69–80.

45. Vokurkova, D.; Vavrova, J.; Sinkora, J.; Stoklasova, A.; Blaha, V.; Rezacova, M. Radiosensitivity of CD3-CD8+CD56+ N K cells. Radiat. Meas. 2010, 45, 1020–1023.

46. Brenu, E.W.; Staines, D.R.; Baskurt, O.K.; Ashton, K.J.; Ramos, S.B.; Christy, R.M.; Marshall-Gradisnik, S.M. Immune and hemorheological changes in chronic fatigue syndrome. J. Transl. Med. 2010, 8, 1.

47. Brenu, E.W.; van Driel, M.L.; Staines, D.R.; Ashton, K.J.; Ramos, S.B.; Keane, J.; Klimas, N.G.; Marshall-Gradisnik, S. M. Immunological abnormalities as potential biomarkers in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. J. Tr ansl. Med. 2011, 9, 81.

48. Brenu, E.W.; van Driel, M.L.; Staines, D.R.; Ashton, K.J.; Hardcastle, S.L.; Keane, J.; Tajouri, L.; Peterson, D.; Ramos, S.B.; Marshall-Gradisnik, S.M. Longitudinal investigation of natural killer cells and cytokines in chronic fatigue syndrom e/myalgic encephalomyelitis. J. Transl. Med. 2012, 10, 88.

49. Hersey, P.; MacDonald, M.; Henderson, C.; Schibeci, S.; D'Alessandro, G.; Pryor, M.; Wilkinson, F.J. Suppression of na tural killer cell activity in humans by radiation from solarium lamps depleted of UVB. J. Investig. Dermatol. 1988, 90, 30 5–310.

50. Hersey, P.; Magrath, H.; Wilkinson, F. Development of an in vitro system for the analysis of ultraviolet radiation-induced suppression of natural killer cell activity. Photochem. Photobiol. 1993, 57, 279–284.

51. de Jonge, K.; Ebering, A.; Nassiri, S.; Maby-El Hajjami, H.; Ouertatani-Sakouhi, H.; Baumgaertner, P.; Speiser, D.E. Cir culating CD56 bright NK cells inversely correlate with survival of melanoma patients. Sci. Rep. 2019, 9, 4487.

52. Simpson, L.O. The role of nondiscocytic erythrocytes in the pathogenesis of myalgic encephalomyelitis/chronic fatigue syndrome. In The Clinical and Scientific Basis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Hyde, B.M., E d.; The Nightingale Research Foundation: Street Ottawa, ON, Canada, 1992; Volume 65, pp. 597–605.

53. Richards, R.S.; Wang, L.; Jelinek, H. Erythrocyte oxidative damage in chronic fatigue syndrome. Arch Med. Res. 2007, 38, 94–98.

54. Saha, A.K.; Schmidt, B.R.; Wilhelmy, J.; Nguyen, V.; Abugherir, A.; Do, J.K.; Nemat-Gorgani, M.; Davis, R.W.; Ramasub ramanian, A.K. Red blood cell deformability is diminished in patients with Chronic Fatigue Syndrome. Clin. Hemorheol. Microcirc. 2019, 71, 113–116.

55. Kozlova, E.; Chernysh, A.; Sergunova, V.; Gudkova, O.; Manchenko, E.; Kozlov, A. Atomic force microscopy study of re d blood cell membrane nanostructure during oxidation-reduction processes. J. Mol. Recognit. 2018, 31, e2724.

56. Nguyen, C.B.; Alsøe, L.; Lindvall, J.M.; Sulheim, D.; Fagermoen, E.; Winger, A.; Kaarbø, M.; Nilsen, H.; Wyller, V.B. Wh ole blood gene expression in adolescent chronic fatigue syndrome: An exploratory cross-sectional study suggesting alt ered B cell differentiation and survival. J. Transl. Med. 2017, 15, 102.

57. Sato, W.; Ono, H.; Matsutani, T.; Nakamura, M.; Shin, I.; Amano, K.; Suzuki, R.; Yamamura, T. Skewing of the B cell rec eptor repertoire in myalgic encephalomyelitis/chronic fatigue syndrome. Brain Behav. Immun. 2021, 95, 245–255.

58. Costa, S.; Borgogna, C.; Mondini, M.; De Andrea, M.; Meroni, P.L.; Berti, E.; Gariglio, M.; Landolfo, S. Redistribution of the nuclear protein IFI16 into the cytoplasm of ultraviolet B-exposed keratinocytes as a mechanism of autoantigen proc essing. Br. J. Dermatol. 2011, 164, 282–290.

59. Wang, H.; Xie, X.; Zhu, J.; Qi, S.; Xie, J. Comprehensive analysis identifies IFI16 as a novel signature associated with overall survival and immune infiltration of skin cutaneous melanoma. Cancer Cell Int. 2021, 21, 694.

60. Dibble, J.J.; McGrath, S.J.; Ponting, C.P. Genetic risk factors of ME/CFS: A critical review. Hum. Mol. Genet. 2020, 29, R117–R124.

61. Ji, S.M. Overexpression of SLC25A15 is involved in the proliferation of cutaneous melanoma and leads to poor progno sis. Med. Sci. (Paris) 2018, 34, 74–80.

62. Boix, E.; Carreras, E.; Nikolovski, Z.; Cuchillo, C.M.; Nogues, M.V. Identification and characterization of human eosinop hil cationic protein by an epitope-specific antibody. J. Leukoc. Biol. 2001, 69, 1027–1035.

63. Conti, F.; Magrini, L.; Priori, R.; Valesini, G.; Bonini, S. Eosinophil cationic protein serum levels and allergy in chronic fat igue syndrome. Allergy 1996, 51, 124–127.

64. Sorensen, B.; Streib, J.E.; Strand, M.; Make, B.; Giclas, P.C.; Fleshner, M.; Jones, J.F. Complement activation in a mod el of chronic fatigue syndrome. J. Allergy Clin. Immunol. 2003, 112, 397–403.

65. Kruckel, A.; Moreira, A.; Frohlich, W.; Schuler, G.; Heinzerling, L. Eosinophil-cationic protein—A novel liquid prognostic biomarker in melanoma. BMC Cancer 2019, 19, 207.

66. Mueller, C.; Lin, J.C.; Sheriff, S.; Maudsley, A.A.; Younger, J.W. Evidence of widespread metabolite abnormalities in My algic encephalomyelitis/chronic fatigue syndrome: Assessment with whole-brain magnetic resonance spectroscopy. Bra in Imaging Behav. 2020, 14, 562–572.

67. Stanculescu, D.; Sepulveda, N.; Lim, C.L.; Bergquist, J. Lessons From Heat Stroke for Understanding Myalgic Enceph alomyelitis/Chronic Fatigue Syndrome. Front. Neurol. 2021, 12, 789784.

68. Sasso, E.M.; Muraki, K.; Eaton-Fitch, N.; Smith, P.; Lesslar, O.L.; Deed, G.; Marshall-Gradisnik, S. Transient Receptor Potential Melastatin 3 Dysfunction in Post COVID-19 Condition and Myalgic Encephalomyelitis/Chronic Fatigue Syndro me Patients. Mol. Med. 2022, 28, 98.

69. Vriens, J.; Owsianik, G.; Hofmann, T.; Philipp, S.E.; Stab, J.; Chen, X.; Benoit, M.; Xue, F.; Janssens, A.; Kerselaers, S.; et al. TRPM3 is a Nociceptor Channel Involved in the Detection of Noxious Heat. Neuron 2011, 70, 482–494.

70. Caterina, M.J. Transient Receptor Potential Ion Channels as Participants in Thermosensation and Thermoregulation. A m. J. Physiol. Regul. Integr. Comp. Physiol. 2007, 292, R64–R76.

71. Okabe, T.; Fujimura, T.; Okajima, J.; Kambayashi, Y.; Aiba, S.; Maruyama, S. First-in-human clinical study of novel tech nique to diagnose malignant melanoma via thermal conductivity measurements. Sci. Rep. 2019, 9, 3853.

72. Wrotek, S.; Brycht, L.; Wrotek, W.; Kozak, W. Fever as a factor contributing to long-term survival in a patient with metas tatic melanoma: A case report. Complement. Ther. Med. 2018, 38, 7–10.

73. Le, M.; Fernandez-Palomo, C.; McNeill, F.E.; Seymour, C.B.; Rainbow, A.J.; Mothersill, C.E. Exosomes are released by bystander cells exposed to radiation-induced biophoton signals: Reconciling the mechanisms mediating the bystander effect. PLoS ONE 2017, 12, e0173685.

74. Blauensteiner, J.; Bertinat, R.; Leon, L.E.; Riederer, M.; Sepulveda, N.; Westermeier, F. Altered endothelial dysfunction-related miRs in plasma from ME/CFS patients. Sci. Rep. 2021, 11, 10604.
75. Brenu, E.W.; Ashton, K.J.; van Driel, M.; Staines, D.R.; Peterson, D.; Atkinson, G.M.; Marshall-Gradisnik, S.M. Cytotoxic lymphocyte microRNAs as prospective biomarkers for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. J. Affect Discord 2012, 141, 261–269.
76. Xu, S.; Ding, N.; Pei, H.; Hu, W.; Wei, W.; Zhang, X.; Zhou, G.; Wang, J. MiR-21 is involved in radiation-induced bystander effects. RNA Biol. 2014, 11, 1161–1170.
77. Xu, S.; Wang, J.; Ding, N.; Hu, W.; Zhang, X.; Wang, B.; Hua, J.; Wei, W.; Zhu, Q. Exosome-mediated microRNA transfer plays a role in radiation-induced bystander effect. RNA Biol. 2015, 12, 1355–1363.
78. Melnik, B.C.; John, S.M.; Carrera-Bastos, P.; Schmitz, G. MicroRNA-21-Enriched Exosomes as Epigenetic Regulators in Melanomagenesis and Melanoma Progression: The Impact of Western Lifestyle Factors. Cancers 2020, 12, 2111.
79. Lai, J.Y.; Luo, J.; O'Connor, C.; Jing, X.; Nair, V.; Ju, W.; Randolph, A.; Ben-Dov, I.Z.; Matar, R.N.; Briskin, D.; et al. MicroRNA-21 in glomerular injury. J. Am. Soc. 2015, 26, 805–816.
80. Zhang, L.; He, S.; Yang, F.; Yu, H.; Xie, W.; Dai, Q.; Zhang, D.; Liu, X.; Zhou, S.; Zhang, K. Hyperoside ameliorates glomerulosclerosis in diabetic nephropathy by downregulating miR-21. Can. J. Physiol. Pharmacol. 2016, 94, 1249–1256.