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EDUCATIONAL ARTICLE

Targeting the Mitochondrial-Stem Cell Connection in Cancer Treatment: A Hybrid Orthomolecular Protocol

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ABSTRACT

The mitochondrial-stem cell connection (MSCC) theory suggests that cancer originates from chronic oxidative phosphorylation (OxPhos) insufficiency in stem cells. This OxPhos insufficiency leads to the formation of cancer stem cells (CSCs) and abnormal energy metabolism, ultimately resulting in malignancy. This concept integrates two well-established theories: the cancer stem cell theory and the metabolic theory. Drawing on insights from molecular biology, pharmacology, and clinical studies, this manuscript introduces a hybrid orthomolecular protocol targeting the MSCC. The protocol includes 7 therapeutic recommendations, consisting of orthomolecules, drugs, and additional therapies. The aim of this hybrid orthomolecular protocol is to achieve additive and synergistic effects to enhance OxPhos, inhibit the primary fuels of cancer cells (glucose and glutamine), target CSCs and metastasis. Thus, numerous experiments suggest that targeting MSCC could be a potential therapeutic approach for cancer treatment.

Keywords: *cancer metabolism; mitochondria; oxidative phosphorylation; cancer stem cells; glucose; glutamine; orthomolecules; repurposed drugs; diet; lifestyle interventions*

INTRODUCTION

Many theories exist regarding the origin of cancer, namely the metabolic theory (Seyfried & Chinopoulos, 2021), the somatic mutation theory (SMT) (Hanahan & Weinberg, 2000), the cancer stem cell theory (Capp, 2019), and the tissue organization theory (Soto & Sonnenschein, 2011). In a recently published study, a new concept was introduced the mitochondrial-stem cell connection (MSCC) (Martinez, et al., 2024). This concept combines the cancer stem cell theory and the metabolic theory. The MSCC theory suggests that cancer arises from impaired oxidative phosphorylation (OxPhos) in one or more stem cells, potentially leading to the formation of cancer stem cells (CSCs) and, consequently, tumorigenesis. This connection between CSCs and mitochondria appears to be crucial at all stages of cancer (Martinez, et al., 2024). The MSCC aligns with the metabolic theory of cancer but specifically focuses on the crucial role of CSCs in every stage of the disease. However, the MSCC differs from the CSCs theory, which typically presents cancer as a genetic disease. Thus, many standard cancer therapies are based on the SMT and generally target the DNA of cancer cells (van den Boogaard, et al., 2022; Sia, et al., 2020). These therapies do not restore OxPhos and sometimes even alter it (Averbeck & Rodriguez-Lafrasse, 2021; Gorini, et al., 2018). Furthermore, standard therapies only target bulk cells but cannot target CSCs (Lytle, et al., 2018), whereas it is CSCs that have the strongest tumorigenic potential (Adams & Strasser, 2008) and are involved in metastasis. This information could partially explain the outcomes observed with the new anticancer therapies. Indeed, Ladanie et al. showed that over the past fifteen years, new therapies have led to an overall survival improvement of 2.4 months (Ladanie, et al., 2020), while Del Paggio et al. reported an improvement of 3.4 months over the past thirty years (Del Paggio, et al., 2021).

Thus, after reviewing the literature on various therapies capable of targeting the MSCC, we selected, based on in vitro and in vivo studies, several orthomolecules, drugs, and additional therapies that have demonstrated an ability to enhance OxPhos, reduce fermentable fuels, and target CSCs and metastasis. Furthermore, when supported by scientific literature, we included case studies of cures using monotherapy in humans. From this combination, we developed a hybrid orthomolecular protocol, which is proposed as a new therapeutic strategy for cancer.

Key Points of the MSCC:

- An alteration of OxPhos may initiate tumorigenesis in one or more normal stem cells, leading to the formation of CSCs (Martinez, et al., 2024).
- The degree of malignancy could be directly correlated with significantly lower mitochondria and lower total respiratory capacity in tumor cells (Elliott, et al., 2012; Pedersen, 1978; Seyfried, et al. 2020).
- In order to grow and survive, cancer cells require the primary fuels glucose and glutamine to compensate for OxPhos insufficiency. The respiratory impairment induces overexpression of oncogenes and inactivation of tumor-suppressor genes, which contribute to abnormal energy metabolism in cancer. To date, no evidence has demonstrated the growth of any tumor cells, including CSCs, occurs with the deprivation of fermentable fuels (glucose, pyruvate, or glutamine) (Lee, et al., 2024; Liao, et al., 2017; Holm, et al., 1995; Mathews, et al., 2014; Pastò, et al., 2014).
- The tumor microenvironment (a consequence of mitochondrial impairment) is characterized by low pH (acidic), hypoxia, entropy, pressure and deformation, increased temperature, stroma, altered rotation of cytoplasmic water, and damped bioelectricity or electromagnetic field (Martinez, et al., 2024).
- Metastasis remains the leading cause of cancer mortality. According to MSCC, it occurs due to fusion hybridization between CSCs and macrophages (Martinez, et al., 2024; Seyfried & Huysentruyt, 2013).

These principles are applicable to all types of cancer.

ORTHOMOLECULAR MEDICINE FOR TARGETING THE MSCC

Vitamin C

The anti-cancer properties of vitamin C have been known for over 50 years (Mussa, et al., 2022). Vitamin C demonstrates cytotoxic effects on cancer cells both in vitro and in vivo (Fan, et al., 2023). In vitro, vitamin C alone is more effective than chemotherapy (cisplatin) alone at inducing apoptosis in colon cancer cells (Wang, et al., 2016). In vivo, vitamin C alone significantly reduces tumor weight and the number of metastases in pancreatic cancer, whereas standard chemotherapy (gemcitabine) alone, commonly

used for pancreatic cancer, increases tumor weight and the number of metastases (Polireddy, et al., 2017). In vivo hepatocellular carcinoma, vitamin C alone reduces CSCs and tumor volume, whereas conventional therapy (cisplatin) alone reduces tumor volume (to a lesser extent than vitamin C) but increases CSCs (Lv, et al., 2018). Vitamin C can directly infiltrate into the tumor intracellular environment, reduce oxidative stress, target the mitochondria of cancer cells, and induce cancer cell death, including metastases (Roa, et al., 2020; Wan, et al., 2021). The alkaline intracellular environment of cancer cells, with a pH between 7.1 and 7.7, maximizes the proliferation of cancer cells (Cardone, et al., 2005; Gillies, et al., 2002). Vitamin C, through its acidic pH, could deactivate the environmental adaptations, having anti-cancer effects by compromising the growth of tumor cells and inhibiting tumor progression (Persi, et al., 2018). It can increase ATP production by increasing mitochondrial electron flux, thereby restoring cellular respiration and apoptosis function (Gonzalez, et al., 2010; Gonzalez, et al., 2023).

Vitamin C can target and eradicate CSCs (Bonuccelli, et al., 2017; Lee, 2023; Satheesh, et al., 2020), and protect against hypoxia and inflammation (Luo, et al., 2022). It can induce apoptosis in drug-resistant cancer cells, and inhibit uncontrolled proliferation of cancer cells and metastatic spread (Butt, et al., 2020). Vitamin C can also cause a polarization of M2 macrophages into M1 macrophages. This could be particularly relevant for inhibiting metastatic spread because M2 macrophages are implicated in metastases (Ma, et al., 2022). High pharmacological intravenous doses of vitamin C have been shown to kill cancer cells but not normal cells (Chen, et al., 2005; Chen, et al., 2008; Ngo, et al., 2019). For example, high doses of intravenous vitamin C may induce apoptotic cell death in tumor cell lines through a pro-oxidant mechanism (Gonzalez, et al., 2010; Kc, et al., 2005; Mussa, et al., 2022).

In normal cells, vitamin C enters mitochondria in its oxidized form via glucose receptors (Glut1) and protects mitochondria from oxidative injury (Kc, et al., 2005). Thus, vitamin C can directly compete with glucose for cellular entry by glucose receptor.

Glycolysis and glutaminolysis have a major role in the metabolism of cancer cells. Vitamin C has the ability to inhibit glycolysis (Aguilera, et al., 2016; Park, et al., 2018; Yu, et al., 2023) and glutamate synthesis (Zeng, et al., 2022). It can specifically limit glutamine synthesis by inhibiting glutamine synthetase (GS), leading to a decrease in the level of glutathione and an increase in reactive oxygen species (ROS) thus resulting in cell death (Long, et al., 2021). GS plays a key role in macrophages and thus in metastases. GS inhibition can reverse the phenotype of M2 macrophages and promote the polarization of M1 macrophages. It will reduce intracellular glutamine and the absorption of glutamine will be channeled, which will eliminate metastases (Wei, et al., 2020). Thus explaining the glutamine dependence observed in advanced cancers (Seyfried, et al., 2020) and confirming the role of vitamin C on metastatic cancers.

The pioneers of intravenous vitamin C cancer treatment, Cameron and Pauling, observed improved survival times for many cancers (lung, stomach, colon, breast, kidney, rectum, and bladder). They observed survival times multiplied by 55 after 1 year, in terminal cancer patients treated with intravenous injections of ascorbate: 22% in the treated group and 0.4% in the control group in patients considered to be incurable following standard treatment. Their intervention consisted of an intravenous injection of 10 g/day for approximately 10 days and orally thereafter (Cameron & Pauling, 1978). The Mayo Clinic attempted to reproduce these results, but intravenous vitamin C was replaced by oral vitamin C and the results were therefore unsurprisingly not reproduced (Moertel, et al., 1985). The plasma concentrations, and therefore the effects of vitamin C, are much lower with oral supplementation (Mikirova, 2017). Several case studies have been published by the Riordan Clinic team and collaborators, reporting cases of tumor regression in patients who received intravenous vitamin C (Riordan, et al., 2000; Riordan, et al., 2004; Sebastian, et al., 2006). Additionally, Li and colleagues showed that when taken regularly, antioxidant vitamins (vitamins A, C and E) could reduce cancer mortality (Li, et al., 2012). However, the antioxidant action of vitamin C should primarily be used in cancer prevention (Deruelle & Baron, 2008), as antioxidants can sometimes promote tumor growth (Long, et al., 2021).

Vitamin D

Vitamin D has shown anti-cancer effects in vitro and in vivo for almost all cancer types (Chakraborti, 2011; Seraphin, et al., 2023). Like vitamin C, it targets the mitochondria by improving metabolism and regulating mitochondrial respiration (Matta Reddy, et al., 2022; Quigley, et al., 2022). Vitamin D can also target CSCs and metastases (Marigoudar, et al., 2022; Wu, et al., 2019), and inhibit glycolysis and glutaminolysis pathways (Sheeley, et al., 2022; Zhou, et al., 2016). It has been observed that daily vitamin D supplementation can reduce total cancer mortality, but this has not been observed for infrequent large bolus doses (Keum, et al., 2022). Cancer patients are often deficient in vitamin D and they can benefit from effective therapy with minimal risk (Hohaus, et al., 2018), including intravenously (Dressler, et al., 1995; Fakih, et al., 2007;

Trump, 2018). One case report details an elderly patient with advanced pancreatic cancer who was unable to undergo chemotherapy, radiation, or surgery. Instead, the patient received a daily dose of 50,000 IU of vitamin D3 for 9 months and experienced an unexpectedly prolonged period of disease-free progression, far exceeding what would have been expected with conventional chemotherapy (Cannon, et al., 2016).

Chandler et al. showed a preventive effect of vitamin D supplementation in patients with a normal body mass index (BMI), demonstrating a 37% reduction in the incidence of metastatic cancer (24 cancers in the vitamin D group and 39 cancers in the placebo group) leading to a reduction in cancer mortality of 42% (38 people in the Vitamin D group and 68 people in the placebo group). The dose utilized was 2000 IU/day, which is the recommended daily intake for a healthy individual (Chandler, et al., 2020). A recent randomized controlled trial on vitamin D supplementation (2000 IU/d vitamin D3 versus placebo) found that gastrointestinal cancer patients who were p53 immunoreactive experienced a significant reduction in relapse or death associated with vitamin D supplementation over nearly six years of follow-up (Kanno, et al., 2023). Meta-analyses of observational studies for at least 12 different cancer types reported the inverse correlations of serum 25-hydroxyvitamin D [25(OH)D] and cancer incidence (Muñoz & Grant, 2022).

Zinc

Zinc supplementation has been recommended as a possible adjunctive treatment for cancer. (Costello & Franklin, 2017; Hoppe, et al., 2021) Zinc specifically protects mitochondria from damage by reactive oxygen species that are generated as by-products of mitochondrial respiration (Zhang, et al., 2018). It has been shown that zinc supplementation induces mitochondrial pyruvate transport, oxidative phosphorylation, and ATP production in both normal and toxic-induced oxidative stress in vitro (Yang, et al., 2017). In human ovarian cancer cells, zinc induces degradation of mitochondria, and restores apoptosis, especially if introduced together with zinc ionophores (Chen, et al., 2020). Zinc can suppress cancer stem cell-like properties of oral cancer and breast cancer cells in vitro (Chu, et al., 2023; Xu, et al., 2022), reduce the expression of markers of cancer cell stemness, and enhance sensitivity to chemotherapy in colorectal cancer cells (Ye, et al., 2022). Excess zinc can irreversibly block energy production of cancer cells, cause NAD+ loss, and inhibit cellular glycolysis (Wu, et al., 2022).

There are a total of 151 publications confirming the link between zinc deficiency and malignancy (Sugimoto, et al., 2024). Zinc deficiency is implicated in many cancers, including oesophageal, liver, lung, breast, colon and others (Lu, et al., 2006; Tamai, et al., 2020; Wang, Y., et al., 2019; Wu, et al., 2015). Zinc shows toxicity toward cancer cells without showing any side effects toward healthy cells and deficiency negatively correlates with survival rates (Gelbard, 2022; Sugimoto, et al., 2024). Similar to vitamin C, zinc may have a specific pro-oxidant effect on cancer cells (Aljohar, et al., 2022).

POTENTIAL DRUGS FOR TARGETING THE MSCC

Several pharmaceutical agents can primarily target genetic pathways associated with CSCs, including Vismodegib, Glasdegib, MK-0752, OMP-54F28, and Selinexor (Zhou, et al., 2021). Other pharmaceutical agents have been proposed to target mitochondria, such as Metformin for OxPhos (Ward, et al., 2017; Zheng, et al., 2023) Doxycycline, Tigecycline, and Bedaquiline for mitochondrial biogenesis; Mdivi-1 drug in mitochondrial dynamics; and 188Re-liposome and the inhibitor liensinine to block mitophagy (Jagust, et al., 2019; Praharaj, et al., 2022). Most of the time, these agents do not restore mitochondrial homeostasis (Liu, Y., et al., 2023), as their specific actions alter or only partly restore dysfunction. The alteration of mitochondrial function with pharmaceutical agents must be considered with caution, as it can be very dangerous for healthy cells (Vuda & Kamath, 2016).

REPURPOSED (OFF-LABEL) DRUGS FOR TARGETING THE MSCC

Ivermectin

An anti-parasitic derived from a bacteria called Streptomyces avermitilis, Ivermectin has anti-cancer properties and induces autophagy and apoptosis of cancer cells (Liu, et al., 2020). Ivermectin has shown a significant impact on various cancer cell lines (Juarez, et al., 2020), inducing apoptosis in cancer cells in vivo (Sharmeen, et al., 2010) and significantly reducing tumor volume compared to a control (Juarez, et al., 2020). It induces apoptosis in cancer cells through mitochondrial mediation (Juarez, et al., 2018; Tang, et al., 2021). Ivermectin can target and regulate the pyruvate kinase muscle isoforms at the last step of glycolysis (Li, et al., 2020). It can inhibit glycolysis inducing autophagy (Feng, et al., 2022), and have a selective a pro-oxidant effect on cancer cells (Wang, et al., 2018). It can

also target CSCs and metastases (Dominguez-Gomez, et al., 2018; Jiang, et al., 2022) and macrophages (Zhang, et al., 2022). In vitro, Ivermectin is more effective at inhibiting CSCs in breast cancer cells compared to chemotherapy (paclitaxel) (Dominguez-Gomez, et al., 2018). In vivo, Ivermectin alone is more effective than standard chemotherapy (gemcitabine) alone at reducing tumor weight and volume in pancreatic cancer (Lee, et al., 2022). Ivermectin is a very safe drug. In healthy volunteers, the single dose was increased to 2 mg/Kg, and no serious adverse reactions were found (Guzzo, et al., 2002). Demonstrated in another study, cancer patients who took Ivermectin at five times the standard dose (up to 1mg/kg) daily for up to 180 consecutive days had no serious adverse effects (de Castro, et al., 2020). In cases successfully treated with a total or partial combination of Ivermectin, dichloroacetate, and Omeprazole (plus Tamoxifen), Ivermectin inhibited tumor growth through mitochondrial dysfunction and led to apoptosis (Ishiguro, et al., 2022).

Benzimidazoles

Another family of drugs called Benzimidazoles holds promising anticancer capabilities including Fenbendazole and Mebendazole. Mebendazole and Fenbendazole are very structurally similar and generally just as effective in cancer (Bai, et al., 2011; Florio, et al., 2019; Schmit, 2013), in both in vitro and in vivo models (Song, et al., 2022). However, only Mebendazole is FDA approved for use in humans (Impax, 2016). Benzimidazoles have anticancer effects through microtubule polymerization, induction of apoptosis, cell cycle arrest (G2/M), anti-angiogenesis, blocking glucose (Son, et al., 2020) and glutamine pathways (Mukherjee, et al., 2023). Apoptosis is induced by mitochondrial injury and mediated by p53 expression (Mukhopadhyay, et al., 2002; Park, et al., 2022). Benzimidazoles also target CSCs and metastases (Son, et al., 2020; Song, et al., 2022) and, thus, the chemoresistant (cisplatin) cancer cells (Huang, et al., 2021). Mebendazole was more potent against gastric cancer cell lines than other well-known chemotherapeutic drugs (5-fluorouracil, oxaliplatin, gemcitabine, irinotecan, paclitaxel, cisplatin, etoposide and doxorubicin) in vitro (Pinto, et al., 2015). Whereas Mebendazole leads to significantly prolonged survival compared to standard chemotherapy (temozolomide) for glioblastoma multiforme in vivo (Bai, et al., 2011).

Mebendazole is established as a safe drug. In pediatric patients with hydatid disease, long-term Mebendazole treatment (50 mg/kg daily for 9–18 months) was demonstrated to be without significant side effects (Göçmen, et al., 1993). Patients receiving 1500 mg/day of Mebendazole for gliomas were also noted to be without toxicity from the drug (Chai, et al., 2021). Patients with treatment refractory gastrointestinal cancer participating in a phase 2 study using individualized doses of Mebendazole, up to 4 g/day, experienced no severe adverse effects (Mansoori, et al., 2021). A case of near-complete remission was reported in a patient with metastatic colon cancer after taking Mebendazole, following a failure of chemotherapeutic agents including Capecitabine, Oxaliplatin, Bevacizumab, Capecitabine and Irinotecan (Nygren & Larsson, 2014). In another case report, a 48-year-old man with adrenocortical carcinoma had disease progression with all systemic therapies. He was prescribed Mebendazole 100mg twice daily, as a single agent. His metastases initially regressed and subsequently remained stable. While receiving Mebendazole as a sole treatment for 19 months, his disease remained stable. He did not experience any clinically significant adverse effects, and his quality of life was satisfactory (Dobrosotskaya, et al., 2011). Similar results have been observed with Fenbendazole, three patients with stage IV cancer (genitourinary malignancies) were treated at a dose of 1,000 mg three times weekly for several months and experienced complete remission of the disease (Chiang, et al., 2021). Two of the three patients had experienced progression of metastatic disease despite several lines of treatment before starting Fenbendazole.

DON (6-diazo-5-oxo-L-norleucine)

DON is a glutamine-specific antagonist more potent than Benzimidazoles. DON has potent antitumor activity in vitro and in vivo (Olsen, et al., 2015). It specifically targets glutamine and also affects glucose uptake (Leone, et al., 2019). DON can specifically induce apoptosis in CSCs (Jariyal, et al., 2021), and target metastases (Shelton, et al., 2010). Low daily doses of DON are without toxicity (Lemberg, et al., 2018).

DIETARY INTERVENTIONS FOR TARGETING THE MSCC

Fasting

Fasting induces an improvement in mitochondrial activity through the increase of OxPhos, autophagy, and the inhibition of glycolysis and glutaminolysis (Bianchi, et al., 2015; Nencioni, et al., 2018; Tiwari, et al., 2022). Fasting can train the regeneration of "normal" stem cells (Mihaylova, et al., 2018), but it can also alter CSCs through autophagy (Nazio, et al., 2019). Inhibi-

tion or deprivation of glucose leads to the death of CSCs (De Francesco, et al., 2018). In vivo, fasting has anticancer effects and enhances the activity of drugs with which it is combined (Nencioni, et al., 2018). Taking into account the molecular mechanisms of cancer growth, researchers have affirmed that "… prescribing fasting as an anticancer drug may not be far away if large randomised clinical trials consolidate its safety and efficacy" (Deligiorgi, et al., 2020).

Ketogenic Diet and Ketone Metabolic Therapy (KMT)

Therapeutic ketosis given as a ketogenic diet or ketone metabolic therapy (KMT) inhibits cancer stem cell growth, restores apoptosis (Ji, et al., 2020), and increases cellular respiration (Greco, et al., 2016). The ketogenic diet exhibits antitumor effects both in vitro and in vivo, primarily by inhibiting the glycolysis pathway in various types of cancer (Weber, et al., 2018; Weber, et al., 2020), and its efficacy has been demonstrated in humans with glioblastoma mutiforme (Elsakka, et al., 2018; Zuccoli, et al., 2010). The maximum therapeutic benefits of DON and Mebendazole occurred only when the drugs were administered together with a ketogenic diet (Mukherjee, et al., 2019; Mukherjee, et al., 2023). Moreover, the association between a ketogenic diet and DON reduces DON toxicity (Mukherjee, et al., 2019). A ketogenic diet or fasting could inhibit the fuels necessary for cancer cells (glucose and glutamine) while also increasing the activity of OxPhos (Bianchi, et al., 2015). A case study reported the survival of a patient with grade IV glioblastoma living more than 6 years after diagnosis, treated with surgical reduction and a ketogenic diet under therapeutic ketosis without chemoradiotherapy (Seyfried, Shivane, et al., 2021). Foster analyzed 200 cases of spontaneous cancer regression, and showed that 87% made a major change in diet, primarily vegetarian in nature, 55% used some form of detoxification, and 65% used nutritional supplements (Foster, 1988). The goal with the ketogenic diet and ketone metabolic therapy is to simultaneously restrict the glycolysis and glutaminolysis pathways while at the same time transition the body into a state of ketosis to target the cancer cells – both CSCs and non-cancer stem cells. In addition to metabolic ketosis, ketone supplementation studies have demonstrated that ketones independently enhance mitochondrial function (Woolf, et al., 2016; Seyfried, et al., 2017) and suppress tumor growth by targeting metastasis and most hallmarks of cancer (Poff, et al., 2014; Poff, et al., 2019).

ADDITIONAL THERAPEUTIC CONSIDERATIONS

Press-Pulse Therapy

Press-Pulse therapy offers two-axis therapy. The "Press" axis, which consists of following a ketogenic diet associated with stress management. And a Pulse axis, which combines inhibition of glycolysis by 2-deoxyglucose (2-DG), inhibition of glutaminolysis by DON (6-diazo-5-oxo-L-norleucine), and hyperbaric oxygen therapy (HBOT) to reverse hypoxia and induce cancer-specific oxidative stress (Seyfried, et al. 2017). The metabolic theory underlying the Press-Pulse therapy is the closest to the proposed MSCC theory.

Physical Activity

Diabetes and obesity are risk factors for many cancers (Grant, 2024), probably through the alteration of OxPhos (Lewis, et al., 2019), promote CSCs (Hillers-Ziemer, et al., 2020) and the increase of the Warburg effect (Zhang & Le, 2021). Thus, physical activity may confer a protective role. Endurance exercises increase the volume of mitochondria, which improves mitochondrial respiration (Baldwin, et al., 1972; Jacobs & Lundby, 2013) and its protective effects on healthy cells (Kolodziej & O'Halloran, 2021). Exercise also decreases glycolytic activity (Gibb, et al., 2017). ATP production and mitochondrial respiration are highest during regular low to moderate intensity training (Flockhart, et al., 2021). Physical activity supports tissue regeneration, in part with stem cells (Liu, C., et al., 2023). Specifically concerning cancer cells, physical activity inhibits their proliferation and induces apoptosis (Wang & Zhou, 2021).

Hyperbaric Oxygen therapy (HBOT)

Hypoxia is a critical characteristic of malignant tumors and involves enhanced cell survival, angiogenesis, glycolysis and glutaminolysis metabolism, and metastasis. There is evidence that implies oxygen is a drug, dependent upon the dose (Poff, et al., 2016) and that HBOT has tumor-inhibitory effects, especially when combined with KMT (Seyfried, et al., 2014). HBOT exhibits potent antitumor activity both in vitro and in vivo, whether used alone or in combination (Moen & Stuhr, 2012). Tumor cells may adapt to ischemic and low nutrient microenvironments by three main adaptations: the angiogenic switch, deregulation of apoptosis, and the metabolism shift (Daruwalla & Christophi, 2006). HBOT can target CSCs and metastases (Liu, et al., 2021; Xiong, et al., 2023) and increase OxPhos

(Hadanny, et al., 2022). KMT is synergistic with HBOT and elicits a potent synergistic effect on suppressing tumor growth and metastatic spread in pre-clinical models of metastatic cancer and human case reports (Elsakka, et al., 2018; Poff, et al., 2015; Poff, et al., 2019).

PROPOSED HYBRID ORTHOMOLECULAR PROTOCOL

Based on our review of the scientific literature, the following protocol combining orthomolecules, drugs and additional therapies for targeting the MSCC in cancer treatment is proposed:

1 Intravenous Vitamin C

Intermediate- and high-grade cancers:
Dose of 1.5g/kg/day, 2-3x per week (Fan, et al., 2023). Established as a non-toxic dose for cancer patients (Wang, F., et al., 2019).

2 Oral Vitamin D

All cancer grades:
Dose of 50,000 IU/day for patients with a blood level ≤ 30ng/mL; 25,000 IU/day for levels 30-60ng/mL; and 5000 IU/day for levels 60-80ng/mL. Established as a non-toxic dose (Cannon, et al., 2016; Ghanaati, et al., 2020; McCullough, et al., 2019).

It is necessary to reach a blood level of 80 ng/mL of vitamin D (25-hydroxyvitamine D (25(OH) D) (Kennel, et al., 2010; Mohr, et al., 2014; Mohr, et al., 2015). This level is non-toxic (Holick, et al., 2011). Once this level is reached it must be maintained with a reduced daily dosage of ≈ 2000 IU/day (Ekwaru, et al., 2014). The vitamin D blood concentration should be measured every two weeks for high doses and monthly for lower doses.

3 Zinc

All cancer grades:
Dose of 1 mg/kg/day is established as a non-toxic dose for cancer patients (Hoppe, et al., 2021; Lin, et al., 2006).

The reference range for serum zinc concentration is 80 to 120 µg/dL (Mashhadi, et al., 2016; Yokokawa, et al., 2020). Once this level is reached it must be maintained with a reduced daily dosage of 5mg/day (Li, et al., 2022). The zinc blood concentration should be measured monthly.

4 Ivermectin

Low-grade cancers:
Dose of 0.5mg/kg, 3x per week (Guzzo, et al., 2002).

Intermediate-grade cancers:
Dose of 1mg/kg, 3x per week (Guzzo, et al., 2002).

High-grade cancers:
Dose from 1 mg/kg/day (de Castro, et al., 2020) to 2 mg/kg/day (Guzzo, et al., 2002).

All these doses have been established as tolerable for humans (Guzzo, et al., 2002).

5 Benzimidazoles and DON

Low-grade cancers:
Mebendazole: Dose of 200 mg/day (Dobrosotskaya, et al., 2011).

Intermediate-grade cancers:
Mebendazole: Dose of 400 mg/day (Chai, et al., 2021).

High-grade cancers:
Mebendazole dose of 1,500 mg/day (Son, et al., 2020) or Fenbendazole 1,000 mg 3x per week (Chiang, et al., 2021).

All these doses have been established as tolerable for humans (Chai, et al., 2021; Chiang, et al., 2021; Son, et al., 2020). Benzimidazoles can be replaced or combined with DON, administered without toxicity; intravenously or intramuscularly: 0.2 to 0.6 mg/kg once daily; or orally: 0.2 to 1.1 mg/kg once daily (Lemberg, et al., 2018; Rais, et al., 2022). Benzimidazole are much easier to obtain than DON. However, for metastatic cancers, which rely heavily on glutamine (Seyfried, et al., 2020), a combination of DON and Benzimidazoles should be considered (Mukherjee, et al., 2023).

6 Dietary Interventions

All cancer grades:
Ketogenic diet (low carbohydrate-high fat diet, 900 to 1500 kcal/day) (Weber, et al., 2020).

Ketone metabolic therapy consists of approximately 60-80% fat, 15-25% protein and 5-10% fibrous carbohydrates. Adequate hydration and single-ingredient whole food ketogenic meals are necessary to achieve a glucose ketone index (GKI) score of 2.0 or below (Meidenbauer, et al., 2015; Seyfried, Shivane, et al., 2021). GKI should be

measured 2–3 hours postprandial, twice a day if possible (Meidenbauer, et al., 2015; Seyfried, Shivane, et al., 2021).
Intermediate- and high-grade cancers:
The ketogenic diet should be coupled with a water fast for 3 to 7 consecutive days in advanced cancers (Phillips, et al., 2022; Arora, et al., 2023). The water fast should be repeated several times (≈ every 3-4 weeks) throughout the treatment (Nencioni, et al., 2018), but fasting needs to be undertaken cautiously in individuals using certain drugs and those with < 20 BMI, to prevent loss of lean body mass. For patients who can not fast, the Fasting-Mimicking Diet (300 to 1,100 kcal/day of broths, soups, juices, nut bars, and herbal teas) can be used (Nencioni, et al., 2018).

7 **Additional Therapeutics**

All cancer grades:
Moderate physical activity, 3x per week. Increased heart and respiratory rate for a period of 45 to 75 minutes (Bull, et al., 2020) with activities such as cycling, running, swimming, etc.

Intermediate- and high-grade cancers or individuals who are unable to engage in physical activity:
Hyperbaric oxygen therapy, 1.5 to 2.5 ATA for 45 to 60 minutes 2-3x per week (Gonzalez, et al., 2018; Poff, et al., 2015).

The protocol should be followed for an average duration of 12 weeks, regardless of cancer type. The analysis of the interactions between each of the molecules revealed no contraindications to the combination of these substances (ANSM, 2023; CRAT, 2024; Lemberg, et al., 2018; Vidal, 2024). The treatment dosage and duration can be adjusted by the physician according to the individual patient, their ability to obtain the various molecules, and the treatment results. Adaptation of the protocol to include additional molecules to restore health, could be considered by the physician. These may include: vitamin K2 (Xv, et al., 2018), vitamin E (Abraham, et al., 2019), coenzyme Q10 (Liaghat, et al., 2024), methylene blue (da Veiga Moreira, et al., 2024), niacinamide (Yousef, et al., 2022), riboflavin (Suwannasom, et al., 2020), Artemisinin + 5-aminolevulinic acid (to cause porphyrin accumulation) (Adapa, et al., 2024), melatonin (Mocayar, et al., 2020), NADH (Medjdoub, et al., 2016), and magnesium (Ashique, et al., 2023), as examples. However, antioxidant dosages should be avoided.

This additive and synergistic effect of this combination of orthomolecules, drugs, and additional therapies targets the MSCC by increasing OxPhos activity in healthy mitochondria, offering protective action for these cells. However, in cancer cells, both CSCs and non-CSCs, the pro-oxidant effect of the combination induces apoptosis. Additionally, this protocol specifically targets fermentable fuels, CSCs and macrophages, and thus metastases. In brief, the key points of the MSCC. Therefore, comparative studies need to be conducted in both animals and humans to evaluate the effectiveness and safety of this hybrid protocol against standard therapies.

CONCLUSION

The mitochondrial-stem cell connection could be a key element in the therapeutic approach to cancer. In light of current knowledge, we have selected and propose the use of specific orthomolecules, drugs and other therapies for their potential to revive cellular OxPhos activity, and target CSCs, glycolysis and glutaminolysis. These are also aimed at addressing metastases created by fusion hybridization between cancer stem cells and macrophages. Numerous experiments in cells, animals, and humans support the role of targeting the MSCC in both the prevention and treatment of cancer.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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