INNSPUB

International Journal of Biosciences | IJB |
ISSN: 2220-6655 (Print), 2222-5234 (Online)
http://www.innspub.net
Vol. 13, No. 1, p. 72-85, 2018

REVIEW PAPER OPEN ACCESS

Oxygen therapy in cancer treatment: progress & promises

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Key words: Tumor-micro-environment, Hypoxia, Therapy-resistance, Oxygen therapy.

http://dx.doi.org/10.12692/ijb/13.1.72-85 Article published on July 15, 2018

Abstract

Low oxygen condition or hypoxia is a distinguishing feature of the tumor microenvironment, which is a well-recognized factor responsible for the limited efficacy of traditional modes of cancer treatments, such as-radiotherapy, chemotherapy and photodynamic therapy. However, oxygen therapy can reverse the hypoxia-mediated de-sensitization of hypoxic tumor cells towards the conventional cancer treatments. The efficacy of photodynamic, drugs or radiation routines is enhanced whenever oxygen therapy is coupled with conventional treatment regimes. Additionally, a significant reduction in tumor mass post-oxygen therapy is evident, irrespective of coupling it with the conventional therapy. Hyperbaric Oxygen therapy (HBOT) was earlier used in cancer treatments. Nevertheless, untargeted application of HBOT comes with severe side-effects. This drawback limits the tumor oxygenation strategy to the pre-clinical stage. However recent studies demonstrate a large number of strategies such as use of manganese oxide based depots for site specific oxygen delivery and breathing of excess of oxygen with reduced time etc., all have been discovered to achieve oxygenation of hypoxic tumor micro environment. This article reviews the important progresses made in the field of oxygen therapy. This study will be helpful in developing new therapeutic methods based on the application of oxygen, which can bypass hypoxia-induced resistance to traditional therapeutic regimes.

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Introduction

The tumor micro-environment comprises of-adjoining blood vessels, fibroblasts inflammatory cells, immune cells and their extracellular matrix, proteins & growth factors. This tumor micro-environment primes cells for carcinogenesis by playing a pivotal role in the complex interplay of genetic and epigenetic fluctuations inside cells themselves (Balkwill, 2012). An abnormal oncogene driven progress of tumor cells in association with a disorganized vascular bed of tumor-micro-environment determines the origin of hypoxia. This unregulated proliferation of tumor cells leads to an imbalance between the oxygen availability & its consumption, which further limits the diffusion of oxygen, hence sustaining hypoxic tumor micro-environment (Michiels, 2016; Forster, 2017).

Tumor hypoxia nurtures other hallmarks of tumor micro environment and provides a favorable atmosphere for carcinogenesis (Gilkes, 2017; Petrova, 2018) while selecting aggressive phenotypes from a heterogeneous tumor cell population (Vaupel, 2004; Rankin, 2016).

Hypoxia induces extensive biological alterations that promote malignancy, such as- increased cellular proliferation, inhibition of apoptosis, de-activation of DNA repair pathways, increased genomic instability, up-regulation of growth factors and facilitation of tumor invasion and metastasis processes (Graeber, 1996; Coquelle, 1998, Yuan, 2000; Rofstad, 2000; Harris, 2002; Subarsky, 2003; Bindra, 2004; Koshiji, 2005; Hubi, 2015; Lindqvist, 2018, Ma, 2018).

These hypoxia-induced adaptations in tumor cells sustain them throughout nutrient deficiency and a hostile environment present during hypoxia (Ackerman, 2014; Leithner, 2017; McNeil, 2017; Sormendi, 2018).

Diminished transport of chemotherapy drugs through the disorganized vascular network of hypoxic tumor micro-environment severely limits their efficacy (Vaupel, 2001; Trédan, 2007; Aouali, 2017).

A number of cytotoxic drugs lose efficacy in the hypoxic environment e.g. cyclophosphamide, carmustine, carboplatin, and melphalan, anthracyclines, mitoxantrone and Etoposide, doxorubicin etc. (Teicher, 1994; Littlewood,2001; Sullivan, 2008; Cosse, 2008; Fu,2014).

Hypoxia is well-established to enable the resistance to radiotherapy as well as photodynamic therapy (Gray, 1953; Luna, 1991; Brizel, 1997; Rofstade, 2000; Ferrario, 2000; Koukourakis. 2001). These therapies include reactive oxygen species-mediated apoptosis, where oxygen is prerequisite for the destruction of tumor cells. Thus, non-accessibility of oxygen in the tumor micro-environment is a restriction for their effectiveness. Both of the approaches are also notorious to intensify the hypoxia by consumption of available low oxygen amount in tumor micro-environment consequently lead to more resistance and low therapeutic potential (Bakalova, 2004; Karimaian, 2017).

Considering the limited efficacy of conventional therapies in low oxygen tumor micro-environment several hypoxia-activated pro-drugs have been developed. Their inactive form changes to active form under reductive metabolism by cellular oxide-reductase. Though, molecular oxygen hinders their conversion into the active form, it marks them specific for hypoxia e.g. N-oxide tirapazamine, PR-104 and TH-302 (evofosfamide), AQ4N (banoxantrone), E09(apaziquone) etc. Among above –explained prodrugs some are under clinical trials and other have failed to beat tumor cells growth at a significant level (Rischin, 2008; Williams, 2009; Guise, 2010; Sun, 2012; McKeage, 2012; Phillips, 2013; Guise, 2014).

Thus, hypoxia is a self-determining prognostic aspect of cancer progression and reduced clinical outcome. The most suitable approach to deal with the problem of hypoxia is an alteration of hypoxic tumor micro-environment by means of oxygen delivery.

In 1966 the Nobel Prize winner Dr. Otto Warburg publicized that ‘’prime source of the cancer is switching of aerobic respiration to anaerobic respiration” clarifying that lack of oxygen is the foremost reason for cancer. Present day developments in cancer biology have proved that his hypothesis was right. Progress in today’s research in respect of oxygenation of tumor micro environment provides insights that oxygen could be a source in treating and defeating cancer. The main motive of oxygen therapy is to enhance the amount of oxygen in tumor micro-environment.

In recent years oxygen therapy based modulation of hypoxic tumor micro-environment has been widely explored to achieve better performance of cancer therapeutics.

Considering the success of oxygen the rapy in cancer treatments, this study was conducted to summarize the progress of oxygen therapy from past to recent advances made in this field. This review aims to provide an overview of beneficial methods, developed to make oxygen delivery possible in the tumor micro-environment and to reflect the promising role of oxygen in cancer therapeutics.

Hyperbaric oxygen therapy (HBOT): an overview

Hyperbaric oxygen therapy is a non-invasive technique uses 100% oxygen greater than the normal atmospheric pressure to enforce in the hypoxic tissue, consequently increases the oxygen supply to the targeted tissue. This process of HBOT is featured by induction of apoptosis, reduction in vascular density and change in gene expression (Gill, 2004; Vaupel,2007; Michieli, 2009).

In 1662 hyperbaric oxygen therapy was introduced first time by the innovation of an airtight chamber named as ‘domicilium' created by a British physician Henshaw, his finding is exceptional because it happened prior to the discovery of oxygen. It was 1930 when a Brazilian physician predicted and demonstrated the benefits of hyperbaric oxygen therapy. However, hyperbaric oxygen therapy is the subject of discussion for cancer prevention from past few decades (Wenwu, 2013; Yan, 2015) and raised a query that whether hyperbaric therapy is advantageous for cancer patients. A significant number of studies are present to validate the negative and positive effect of HBOT on cancer growth, since studies have long focused to elucidate the effect of HBOT in cancer prevention. Studies in support of hyperbaric oxygen therapy have shown a positive relation in hyperoxia and elevated levels of reactive oxygen species (ROS), consequently lead to cellular damage (Thom,2009).

Studies on the molecular mechanisms of HBOT-induced cell death, disclose a complex signalling network comprises of protein kinases and receptors such as RAGE, CXCR2, TLR3, and TLR4 (Gore, 2010). HBOT also found to regulate the pro-apoptosis and anti-apoptosis pathways (Chen, 2007).

This study was complemented by the induction of apoptosis in osteosarcoma cells & two different animal models, including mammary and gliomastumors after implementation of HBOT in hypoxia (Raa, 2007; Kawasoe, 2009; Moen, 2009).In vivo with in vitro studies on HBOT have publicized the decreased cell proliferation, with a negative effect on histology (Feldmeier, 2003;Stuhr, 2004; Granowitz, 2005; Daruwalla, 2006; Stuhr, 2007; ZhENG-RoNG, 2010).

Anti-angiogenesis and pro-angiogenesis both types of effect of HBOT have been supported by ample of studies(Chong, 2004; Shi, 2005; Heys, 2006; Raa, 2007 Schonmeyr, 2008; Tang, 2009; Kawasoe, 2009; Thom, 2011). In 2012 Moen *et al.* has carried out a research based on a review of the literature to clarify that inconsistencies in response to HBOT are followed by the cancer type and the protocol to be used for HBOT (Moen, 2012).

As HBOT is studied to enhance the oxygen level and induce cell death in a hypoxic tumor. Though, the side effects of HBOT involve more risk than the benefits achieved from it, including oxygen toxic seizures (Seidel, 2013).

In addition, other side effects encompass reversible myopia, epileptic fits etc. (Overgaard, 1989; Leach, 1998).

Thus the approach has not been very successful in solving the problem of oxygen delivery in hypoxia.
HBOT in concomitant with other therapies has given improved outcomes. For example, a study conducted on mice showed an enhanced HBOT-mediated buildup of 5-FU in the kidney & liver tumor-bearing mouse (Takiguchi, 2001). Previously it has also been reported with taxol and doxorubicin. The combined effect of HBOT with photodynamic therapy and radiotherapy was also encouraging (Siemann, 1986;Kalns, 1998; Maier, 2000; Chen, 2002; Petre, 2003; Huang, 2003).

Other approaches used for oxygen delivery include the use of perfluorochemical emulsion, change in haemoglobin-oxygen affinity (Rockwell, 1985; Jain, 2014). Although these discussed methods of tumor oxygenation are confined to pre-clinical studies, none of them extended to the level of clinical testing.

Vascular-normalization and oxygenation of tumor microenvironment

As discussed before solid tumors are characterized by the disorganized vascular bed, which lead towards a hypoxic tumor micro-environment. This hypoxic tumor micro-environment is accountable for the limited efficacy of therapeutic approaches. To improve the potential of therapeutics research has targeted to vascular normalization.

In 1971 it was the first time when anti-angiogenesis therapy was suggested for cancer prevention and it took 1976 to apply this method. Anti-angiogenesis therapy was administered for the vasculature normalization to enhance the efficacy of therapeutics by enhancing the oxygen level in the tumor micro-environment. Vascular normalization is a process involving trimming of incompetent blood vessels, by abolishing extra endothelial cells. The hypothesis of vascular normalization by anti-angiogenesis therapy would be an outcome with improved oxygenation was evidenced by the survival benefits in patients with colorectal, lung, renal, breast, brain and other cancers (Sorensen, 2009; Garcia-Foncillas, 2012; Batchelor, 2013; Emblem, 2013; Vasudev, 2014; Heist, 2015; Jayson, 2016).

Blocking of vascular endothelial growth factor (VEGF) or receptor of (VEGFR2) was one of the methods of anti-angiogenesis therapy, implicated for the vascular normalization. This method was resulting in reduced interstitial fluid pressure with increased oxygen tension in some tumors (Yuan, 1996; Tsuzuki, 2000; Kadambi, 2001). This discovery was consistent with the use of monoclonal-antibody against VEGFR-2 (Hansen-Algenstaedt, 2000). Overexpression of histidine-rich glycoprotein in solid tumors is another one example to justify the connection of vascular normalization and elevated oxygen level of the tumor micro-environment (Rolny, 2001). Other anti-angiogenesis therapies have also been used such as extraction of hormone from a hormone-dependent tumor was also diminished the level of VEGF in tumor cells (Jain, 1998). Anti-angiogenesis therapy was not found completely effective as the proliferation of non-responsive tumor cells is able to regain the aberrant vasculature by producing angiogenic factors (Viloria-Petit, 2001). Currently, this field is moving towards the re-arrangement of tumor vasculature to achieve the better efficacy of therapeutics (Stylianopoulos, 2018).

Recent movements in the field of oxygen therapy

Oxygen is indispensable for the life, needed for breathing and energy production in cells. Although tumor micro-environment is marked with lack of oxygen and rely on anaerobic energy production pathway. Hypoxia is a main driving force for cancer resistance, reversing this hypoxia by means of oxygen delivery seems a promising approach toward the war against cancer. Though current attention in cancer therapy focuses on the application of oxygen therapy.
Recently Michail Sitkovsky, an immuno-physiology researcher at Northeastern University has postulated in his study on the mouse model that, breathing oxygen in excess of 21% (available in the normal environment), could support the immune system to fight tumor development (Hatfield, 2015).

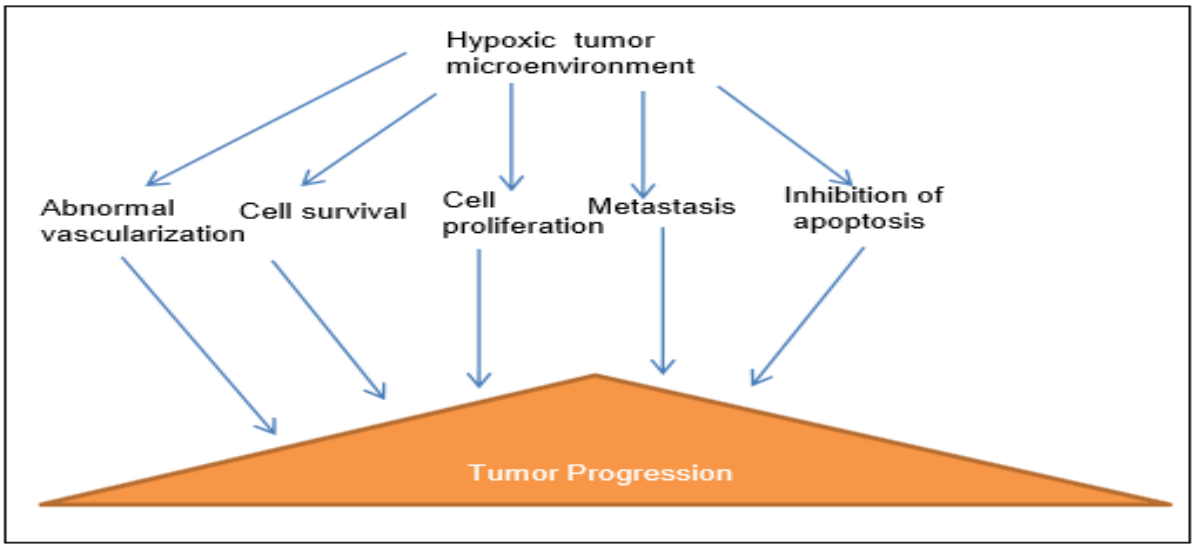

Fig. 1. Hypoxia is an attribute of solid tumors, involved in multiple pathways to support tumor progression (Ruan, 2009).

Effect of oxygenation on tumor regression was demonstrated by the amplified level of oxy-haemoglobin, where exchanging the respiration gas from hypoxic to hyperoxic even for 10 minutes was resulting in increased tumor oxygenation subsequently changes the volume of a tumor after chemotherapy. This study is further going on with reduced time of respiration, would be a step forward to achieve clinical application (Lee, 2018).

Improved oxygen pressure and reduced proliferation of glioma cells were observed with the combined effect of hyperbaric oxygen therapy and nimustine a compound with antineoplastic activity (Lu, 2016). Another study clarifies that a controlled dose of HBOT must be used for beneficiary effects; otherwise, it lead towards tumor survival (Sengupta A, 2018).

For the first time to enhance the effect of chemo-radiotherapy in hypoxictumor micro-environment, an oxygen-based method has developed by using MnO2 and paclitaxel nanoparticles (ANPs-PTX),MANPs-PTX were obtained as final functional Nano-platform. This nano-platform has revealed the great potential for the improvement of chemo-radiation therapy by the production of abundant oxygen needed for tumor oxygenation (Meng, 2018).

Photodynamic therapy is also considered as a promising method in cancer treatments. However, the lack of oxygen is also a major restrictive issue for photodynamic therapy. Recently, tumor-micro-environment accessible Ce6-MnO2/CNTs (CMCs) nano platform was created, with self –oxygen generation property to improve photodynamic therapy. This nano platform reacts with endogenous H_2O_2 to produce singlet oxygen in tumor micro-environment, which effectively augments the effect of photodynamic therapy on tumor growth suppression (Yin, 2018).Similar results were obtained with the synchronous delivery of photosensitizer and oxygen, made possible by using biocompatible liposomes loaded with oxygen carrier haemoglobin and photosensitizer indo-cyanine green. Delivery of liposomes in tumor micro-environment enhances the photodynamic therapy with a down-regulated level of HIF-1alpha and VEGF (Guo, 2018).

The similar combination of oxygen-carrier and photosensitizer has been used with artificial red blood cells to achieve enhanced photodynamic therapy (Luo, 2016). On the other hand, bone marrow-derived monocytes were also used to perform co-delivery of oxygen & photosensitizer offers great potential for the improved efficacy of photodynamic therapy (Huang, 2015).

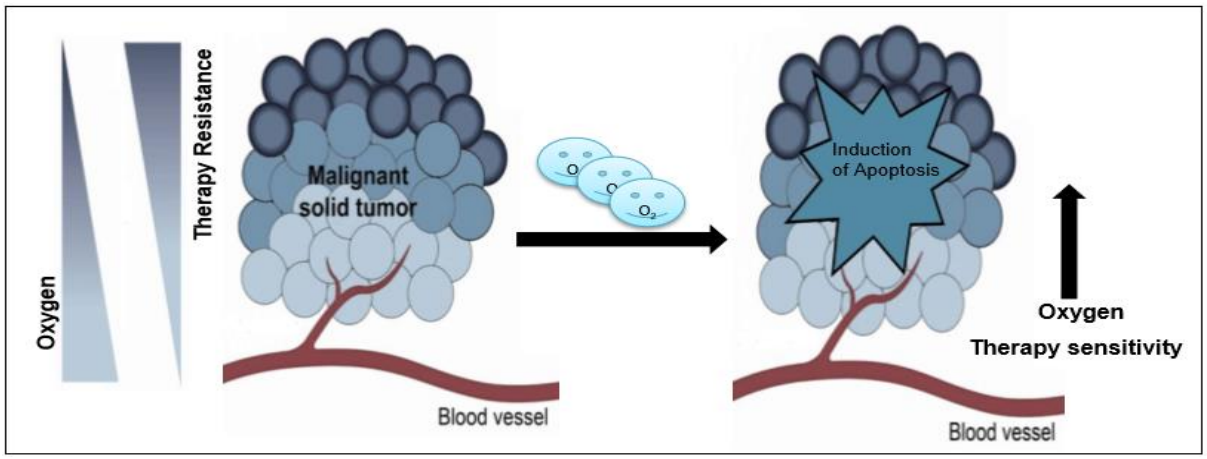

Fig. 2. Pictorial representation of oxygenation of the hypoxictumor microenvironment, leading to induction of apoptosis and also increases the sensitivity of therapy (Brown, 1999; Thomas, 2013).

Previously hyperbaric oxygen therapy (HBOT) was applied to disturb the hypoxia-induced resistance to DOX an anti-tumor drug. This approach fails to get success, as HBOT intensify the ROS-mediated cytotoxicity of DOX toward the normal tissue. For further improvement, an implantable oxygen-generating depot has used to target hypoxic tumor microenvironment. Implantation of oxygen generating depot has given a significant improvement in site-specific cytotoxicity of DOX (Huang, 2016). Ultrasound beam guided oxygen encapsulated nanobubbles were used in MB49murine urothelial carcinoma model has shown to enhance the efficiency of mitomycin-C, resulting in significantly lower tumor progression (Bhandari, 2018).

To defeat the hypoxia-related resistance particularly in photodynamic therapy and radiation therapy innovative oxygen based strategy has been tested in mice, where high oxygen-dissolving property of perfluorocarbons (PFC) was applied intravenously into the mice breathing under hyperoxia. Ultrasound stimulation made PFC nanodroplets to form a circulation of oxygen between lung and tumor, subsequently enlarge the oxygen level of a tumor with improved therapeutic results of radiation and photodynamic therapy. This kind of strategy would be helpful in promoting oxygenation in different tumor models (Song, 2016).

Other studies proposed that inhibition of cellular oxygen consumption could be an effective approach for oxygenation of tumors. Metformin an anti-diabetic drug showed the improved oxygenation in a tumor as it causes a reduction in oxygen consumption by inhibiting the mitochondrial complex I. A meta-analysis with metformin has revealed a significant reduction in breast cancer, colorectal cancer pancreatic cancer, and liver cancer (Zannella, 2013; Zhang, 2013).

Other oxygen therapies to be considered are-
Prof. Keith Scott-Mumby faculty at California Institute for Human Science has published his article explaining the connection of cancer and oxygen. He suggested that in addition to hyperbaric oxygen therapy, oxygen flooding can be used to increase the oxygen level of tumors.

Oxygen flooding includes the use of peroxide and Ozone; both of two substances are able to deliver a high amount of oxygen. But the use of this method imperfectly can be dangerous. Discovery of an alternative method to achieve oxygen flooding would be a path towards success.

Conclusion

Tumor hypoxia is a major concern in the tumor biology, due to its crucial role in resistance to conventional therapies. Oxygen therapy can have long-term as well as short -term effects on tumor hypoxia.

This study reviewed the most beneficiary methods ranging from the breathing of excess of oxygen to enhanced efficacy of conventional therapies in presence of oxygen, which have shown an inhibitory effect of oxygen on tumor growth and also reflects its promising role in cancer prevention. Nowadays research is focused on the vascular re-arrangement for oxygenation of tumor micro-environment. To achieve the tumor regression by decreasing the exposure timing of HBOT is one of the targets of current research. Other future challenges in HBOT cover efficient targeting of hypoxic tumors after its systemic induction. The increasing application of oxygen requires a constant and extended research to achieve the clinical phase of the treatment.

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