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Editorial

Cold Atmospheric Plasma and Oxidative Stress: Reactive Oxygen Species *vs*. Antioxidant

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Editorial

A noteworthy obstacle in treating cancers is selectivity, which implies the protecting surrounding normal tissue, while exclusively inducing cell death of cancer cells within a tumor [1]. Although an advancement is being made in developing treatments that are selective for cancer cells, any given tumor treatment prompts the damage to normal cells inside influenced tissues, which remains a noteworthy issue in oncology. The new field of plasma medicine is a quickly developing and creative interdisciplinary endeavour encompassing plasma physics, life sciences, biochemistry, engineering and clinical medicine [2]. An important feature of cold atmospheric plasma is its ability to produce a mixture of biologically active agents, such as Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), while remaining close to ambient temperature, which enables its safe application to living cells and tissues. All life forms, with the exception of some anaerobic and aerotolerant species, need O_2 for efficient production of energy by the utilization of electron transport chains that at last give electrons to O_2. Because of the biradical nature molecular oxygen, it's readily accepts unpaired electrons to give rise to a series of partially reduced species collectively known as reactive oxygen species [3]. These ROS which are included in initiation and propagation of free radical chain reactions and are potentially highly damaging to cellular targets including DNA, lipids and proteins [4]. In healthy aerobes, production of ROS is approximately balanced with antioxidant defense systems. Having too many ROS in relation to the available antioxidants is often said to be a state of oxidative stress [3]. Oxidative stress can be defined as the imbalance between cellular oxidant species production and antioxidant capability [5]. ROS are well recognized for playing a dual role as deleterious and beneficial species. ROS are harmful in excess, but some level of them is necessary for important cellular functions. Some cells produce ROS to kill invading microbes, and ROS are involved in cell signalling [4,6]. ROS can modify many intracellular signalling pathways including protein phosphatases, protein kinases, and transcription factors, suggesting that the majority of the effects of ROS are through their actions on signalling pathways rather than via non-specific damage of macromolecules; however, exact mechanisms by which redox status induces cells to proliferate or to die, and how oxidative stress can lead to processes evoking tumor formation are still under investigation [3,4]. In a balanced cell state, ROS are produced as a by-product of metabolic processes. The level of ROS can be controlled with antioxidants, such as small molecular weight dietary supplements, including vitamin E and vitamin C; small molecular weight peptides and cofactors, including glutathione and pyruvate; and enzymes, including superoxide dismutase and catalase [7]. In a state of cellular imbalance, in which the levels of oxidants outweigh the levels of antioxidants, damage is caused to nuclear and mitochondrial DNA, proteins, and lipids. If this damage is irreparable, then injury, mutagenesis, carcinogenesis, accelerated senescence, and cell death can occur [7]. Oxidative stress has been linked to diseases, including some allergic and inflammatory skin diseases [8], Alzheimer's [9] and atherosclerosis in diabetes patients [10].Oxidative stress has long been implicated in cancer development and progression [11], suggesting that antioxidant treatment may provide protection from cancer [12]. On other hand, prooxidant therapies, including ionizing radiation and chemotherapeutic agents, are widely used in clinics, based on the rationale that a further oxidative stimulus added to the constitutive oxidative stress in tumor cells should, in fact, cause the collapse of the antioxidant systems, leading to cell death [13]. On the other hand, among the enzymatic systems involved in the maintenance of the intracellular redox balance, a main role is played by Glutathione(GSH) [14] that participates, not only in antioxidant defense systems, but also in many metabolic processes [15]. Elevated GSH levels are observed in various types of tumors, and this makes the neoplastic tissues more resistant to chemotherapy [16,17].Moreover, the content of GSH in some tumor cells is typically associated with higher levels of GSH-related enzymes, such as γ-Glutamylcysteine Ligase (GCL) and γ-Glutamyl-Transpeptidase (GGT) activities, as well as a higher expression of GSH-transporting export pumps [17,18]. The increase in GSH levels, GCL activity and GCLC gene transcription is associated with drug resistance in tumor cells [19,20]. The increase in GSH is a major contributing factor to drug resistance by binding to or reacting with, drugs, interacting with ROS, preventing damage to proteins or DNA, or by participating in DNA repair processes. In melanoma cells, GSH depletion and GGT inhibition significantly increased cytotoxicity via oxidative stress [21]. In addition, it has been demonstrated that GGT-over expressing cells were more resistant to hydrogen peroxide [22] and chemotherapies, such as doxorubicin [23], cisplatin [19], and 5-fluorouracil [24]. Consequently, GSH plays an important role in determining the sensitivity of cells to radiation and drug-induced cytotoxicity [25]. Multidrug and radiation resistance of many tumors, as compared with normal tissues, appears to be associated with higher GSH levels in the cancer cells [26]. Approaches to cancer treatment based on the regulation of GSH concentrations in a tumor must take into consideration the glutathione status and the rate of GSH synthesis in cancer cells [27].Conventional anti-cancer therapies often work well initially, leading to rapid shrinkage of the tumor or tumors. However, it is not uncommon that this initial effectiveness is relatively short-lived. The major problem with current therapies is

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the development of treatment-resistant cells, leading to regrowth of tumors, metastasis, and mortality in many cases. Tumor adaptation to oxidative stress-inducing therapies such as radiation and many chemotherapies is commonly invoked as a primary cause of resistance [28]. The way that plasma oncology depends on oxidative stress suggests that plasma treatment could lead to similar problems with resistance. However, there are hints that RON implicated in plasma oncology could eliminate this resistance. On the other hand, cold atmospheric plasma treatment induces cell cycle arrest in low doses and apoptosis in medium doses. These impacts appear to be mediated by Reactive Oxygen Species (ROS).The present improvements in this field demonstrate the possibilities of this new approach to the construction of new plasma apparatuses for medical applications including endoscopic apparatuses and combined approaches in the adjuvant tumors therapy including plasma mediated drug delivery and drug action.

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