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Short Commentary Open Access

# Cold Atmospheric Plasma as an Alternative Therapy for Cancer Treatment

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## Abstract

Although several cellular and immune based therapies are available, cold atmospheric plasma (CAP) is gaining importance due to its functional ability to accelerate and promote apoptosis of tumour cells. The ionized jet of plasma has been shown to selectively obliterate the tumour cells while leaving the normal healthy cells unaltered. This important property of CAP has been studied in vitro and in vivo. However, there are very few reports and scientific advancements to address the mechanism by which CAP induces cell death. The cellular and molecular mechanisms triggering the events have not been well understood. While changes in the redox potential may be a factor, the role of receptors, cell adhesion molecules, chemokines and cytokines and the apoptotic proteins and various downstream signalling targets are currently being studied. New findings have suggested that the CAP activated medium itself serves as a source for cell stress induced changes in redox potential. It is interesting that CAP may induce the activation of specific receptors, cytokines that may induce cell death. The field of biomarker discovery in combination with CAP may serve as therapeutics treatments for solid tumours and for treatments in cancer biology. Therefore, application of CAP for the purpose of human therapeutics in treatment for cancer serves as a new biomedical intervention that can replace-to-reduce the chemotherapeutic targets.

**Keywords:** Cold atmospheric plasma; TRAIL; TRAIL-R1; CAP; Apoptosis; Cancer stem cells; Plasma medicine

## Commentary

In the recent years, alternative therapy for treatments for cancer has become more popular. Several cellular and immune therapies have gained advancement in the field to reduce the chemotherapeutic dose to patients with various types of cancers. However, excision and recurrence of tumour is still dependent on the chemotherapeutic drugs and recombinant antibodies. A new technology that is gaining more importance in the field of cancer biology is the application of the ionized gas in the form of cold atmospheric plasma CAP for anti-tumour therapy (1,2). Application of CAP has been in practice in dentistry, as antimicrobial and more recently in cancer (3). Several cell lines have been tested in vitro and in vivo including breast cancer and glioblastoma for the cell viability after treatments with CAP and these studies suggested circuitously that the tumour cells either do not proliferate due to arrest in cell cycle and therefore not viable (4).

The gold standard for all plasma researchers is based on the redox efficiency of CAP on the tumour cells. Our laboratory has been using a multiple variety of tumour cell lines, primary tumour stem cells to demonstrate the specificity of the species and to distinguish if it is reactive oxygen or nitrogen species (ROS/RNS) that promotes cell death and anti-tumour activity. While the ROS has been widely acclaimed to cause cell stress and initiate the apoptotic signals, apoptotic proteins like Parp and caspases were shown to be activated within 2minutes of treatments with CAP in vivo and in vitro (5). In our hands for the first time we report that use of CAP in ocular retinoblastoma tumour cells and that CAP-induced cell stress was initiated within 1min (1.4Watts) leads to 100% cell death within 48hours. We also observed similar results in human colon stem cells, cell lines and in breast cancer cell lines. There was a significant difference in the viability and apoptotic phenotype between healthy normal cells and tumor cells with exposure to CAP leading to cell death only in tumor cells and with no effect on the live health cells (data not shown). Therefore there is sufficient supporting evidence to suggest that CAP restored the responsiveness on tumour cells.

The interesting feature of CAP is the selective effect only on the tumour cells and not on the healthy normal cells. It has now been widely approved and accepted that CAP-induced cell stress was evident in various tumour cell lines tested but not unaltered in the normal cell lines(6). These results from various laboratories including our own indicate specificity of CAP as targeted therapeutic alternative in the field of cancer biology.

Although numerous treatments for anti-cancer therapy have been augmented, the use of CAP along with these chemotherapeutic drugs may have better effects and applications. While, chemokines, monoclonal antibodies like VEGF have been used (7), there is no striking reports evidence in literature to identify one single molecule that triggers cell death and apoptosis in the presence of CAP. Some researchers have suggested and indicated the report of NF-Kb activation and initiation of caspases (1,4). However, the molecular mechanisms underlying the activation of various signalling molecules, pathways and their therapeutic domain that marks anti-tumor efficacy have to be extensively studied. We demonstrate and hypothesize that there are specific receptors that are triggered in the presence of CAP, like the TRAIL-1 (tumour necrosis factor (TNF)-related apoptosis-inducing ligand) receptor molecule which are responsible to initiate the cell death and apoptosis. Moreover, TRAIL-mediated cell therapies are available and have been used in treatments for breast cancer (8). It is interesting that CAP alone could trigger death inducing signals selectively in the metastatic tumor cells and not in the normal healthy cells by accelerating the TRAIL-R1 expression and induce apoptosis (data not shown). We propose a new therapeutic alternative using

CAP that can replace or reduce the dose of chemotherapeutic drugs like TRAIL. TRAIL mediated cell death and therapies are available and are known to harness either through p53 mediated DNA damage or proteosomal pathways (8,11). The mechanism by which CAP affects the cells at the cell membrane or cell-cell junctions in order to trigger the apoptotic cascade or if CAP is responsible in inducing DNA nick and affect p53 transcription is not very clear (Figure 1).It is a possible hypothesis that there may be autocrine and/or paracrine signalling mechanisms involved in initiating the apoptotic cascade (Figure 1), which are important questions that have to be addressed in plasma medicine. The molecular and biochemical regulators of CAP in inducing selective ablation of tumour cells, therefore seems to be more critical and important application in cancer biology. Biomarker discovery in the field of plasma medicine holds the future of personalized therapeutics for cancer patients, due to the vital application of CAP. Cumulatively, the current trend suggests that CAP could replace chemotherapeutic applications or can selectively reduce the dose otherwise used in antitumor therapy and regenerative medicine.

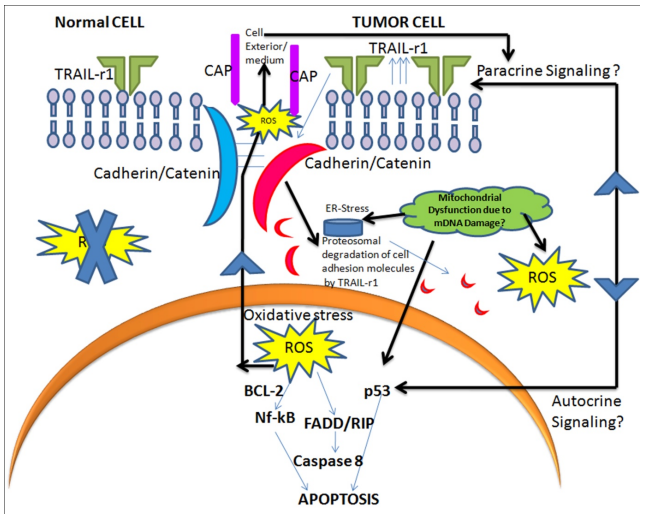


**Figure 1:** A hypothesis showing Cold Atmospheric Plasma via Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)-pathway. In presence of CAP, tumor cells express elevated levels of TRAIL-receptor 1 and thereby triggering the apoptotic signals via paracrine mechanisms to the neighbouring cells. ROS generated may trigger the cell-cell adhesion molecules via proteolytic degradation. Mitochondrial cells stress may induce DNA damage and thereby leading to cell death via TRAIL mediated NF-kb apoptotic pathways. Note the absence of ROS in the normal cells in the presence of CAP. ©US Patent Innovations(USPI), Maryland.

The biological applications of CAP are still in its nascent stages of development. Several unanswered questions in regenerative biology include if CAP helps the normal cells in the wound healing mechanisms While very few reports indicate that cell-cell adhesion and migration are affected by CAP and that it promotes basement membrane associated proteins in wound healing mechanisms in vivo (9), it is imperative to study specific regulating proteins that are involved in cell migration and in stem cell biology (10) to address the CAP mediated mechanisms in cell-based therapies that will serve as personalized therapy and in regenerative medicine.

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