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Potential of Cold Atmospheric Plasma to Stimulate the Development of Arrested Stem Cells

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ABSTRACT

Introduction: Stem cell developmental arrest is a major challenge in regenerative medicine and tissue engineering, often linked to oxidative imbalance, metabolic quiescence, or mitochondrial dysfunction. Although various strategies have been explored, few have succeeded in reactivating arrested stem cells without inducing genomic or epigenetic instability. Cold atmospheric plasma (CAP), an ionized gas at near-room temperature containing reactive oxygen and nitrogen species (RONS), photons, and electromagnetic fields, has emerged as a promising bio-stimulatory tool. Controlled exposure to CAP can modulate redox signaling, enhance mitochondrial activity, and promote cell proliferation and differentiation in mammalian systems. The mild oxidative eustress generated by CAP is hypothesized to restore redox balance and metabolic fluxes, potentially reactivating dormant or developmentally arrested stem cells. This study evaluated the effects of CAP on cell viability, mitochondrial potential, and the expression of pluripotency and differentiation markers to assess its potential as a non-invasive reactivation strategy.

Materials and Methods: Relevant studies were retrieved from Web of Science, PubMed, Google Scholar, SID, and Magiran without time restrictions. Articles that were consistent with study's aim were included.

Results and Discussion: Recent evidence indicates that CAP functions as a dose-dependent bio-stimulant in stem cell systems. It has also been reported that low-dose CAP enhances cell proliferation and upregulates pluripotency markers, such as *OCT4*, *SOX2*, and *NANOG*. In contrast, high-intensity exposure can lead to oxidative damage and apoptosis, emphasizing the importance of dose optimization. CAP activates ERK and PI3K/AKT pathways—key regulators of stem cell survival, proliferation, and differentiation. The mild oxidative eustress mediated by RONS induces adaptive responses that improve mitochondrial function and restore redox homeostasis. Further studies demonstrate that CAP increases mitochondrial membrane potential, boosts ATP synthesis, and upregulates antioxidant enzymes, including *SOD2* and *GPX1*, collectively reactivating metabolic processes in quiescent or arrested cells. At the molecular level, CAP transiently modifies membrane proteins and surface oxidation states, enhancing receptor-mediated signaling and cell–cell communication—factors that are critical for developmental reactivation. Controlled CAP exposure also improves cytoskeletal organization and chromatin remodeling, supporting the transition from a dormant to an active proliferative state.

Conclusion: Our findings suggest that CAP can reactivate developmentally arrested stem cells by creating a balanced redox microenvironment, stimulating mitochondrial metabolism and reinitiating essential developmental pathways. However, the distinction between beneficial eustress and harmful oxidative stress is narrow, highlighting the need to precisely optimize plasma parameters such as power, duration, and gas composition. CAP offers a promising non-invasive approach for rejuvenating arrested or metabolically inactive stem cells, potentially advancing next-generation regenerative therapies.

Keywords: Biophysics, Cold atmospheric plasma, Stem cells

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