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Cold Atmospheric Plasma and Tumor Microenvironment

Mohammad Ismail Akbari

Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Introduction: Genomic analyses show that only ~1–2% of the human genome is responsible for coding proteins, while the remaining ~98% consists of noncoding DNA. This noncoding DNA plays a crucial role in regulating gene function via epigenetic mechanisms (e.g., DNA methylation, histone modification, chromatin remodeling, and noncoding RNAs). Thus, nearly the entire genome contributes to dynamic gene regulation rather than to coding sequences. The presentation emphasizes the tumor microenvironment (TME) as a driver of cancer behavior. In particular, cancer-associated fibroblasts (CAFs)–fibroblasts activated by tumor secretions–are abundant in the TME and actively promote tumor growth, angiogenesis and metastasis. Unlike normal fibroblasts, CAFs remain chronically activated due to signaling from cancer cells. A “recurrence paradox” is noted: even after complete surgical removal of a tumor, microscopic residual tumor cells can persist within this permissive, pro-tumorigenic milieu. Thus, factors within the TME (such as hypoxia, extracellular matrix remodeling, and CAFs) contribute to therapy resistance and disease relapse. Hypoxia is highlighted as a key microenvironmental factor. Low oxygen levels stabilize HIF-1α, a transcription factor that drives a metabolic shift toward glycolytic (known as the “Warburg” effect) in cancer cells. HIF-1α upregulates genes that code for glucose transporters, glycolytic enzymes and angiogenic factors, enabling tumor cells to survive despite inefficient energy production. Hypoxia-induced HIF signaling enhances epithelial-mesenchymal transition, invasion, and therapy resistance. As a result, hypoxic niches enhance cancer stem cell properties and diminish the effectiveness of chemo/radiotherapy. Cold atmospheric plasma (CAP) is presented as an innovative therapy for oncology. CAP generates reactive oxygen and nitrogen species that selectively kill cancer cells while sparing normal tissue.

Materials and Methods: In preclinical and early clinical models, the use of intraoperative CAP in the surgical cavity led to a reduction in reduced epithelial-mesenchymal transition and cancer stem cell markers, an increase in apoptosis and local inflammation, and a notable decrease in CAF density (e.g., by inhibiting fibroblast activation protein).

Results and Discussion: In a recent Phase I trial, the Canady Helios CAP scalpels showed no added toxicity and effectively preserved healthy tissue, achieving excellent local control rates when combined with tumor resection.

Conclusion: This translational summary connects genomic/epigenetic aspects of cancer biology with factors in the TME (such as CAFs, hypoxia/HIF-1α, and metabolic reprogramming). It proposes CAP as a novel adjuvant therapy. Our perspective underscores the clinical importance of targeting not only cancer cells but also their supportive microenvironment to overcome therapy resistance.

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Corresponding Author: Amir Hossein Sameni
Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; E-mail: M.E.Akbari@yahoo.com

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