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Short Communication

Mechanistic Insights into Therapy-Induced Senescence and Secondary Malignancy Risk

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DESCRIPTION

Cancer therapy, including chemotherapy, radiotherapy, and targeted therapy, aims to eradicate malignant cells and improve patient survival. While these modalities have significantly enhanced clinical outcomes, they are often accompanied by unintended cellular consequences. One such consequence is Therapy-Induced Senescence (TIS), a stable growth-arrested state induced in cancer and normal cells following exposure to genotoxic stress. TIS represents a double-edged sword: while it contributes to tumor suppression, senescent cells can also secrete pro-inflammatory and pro-tumorigenic factors collectively termed the Senescence-Associated Secretory Phenotype (SASP), which may increase the risk of secondary malignancies. Understanding the mechanisms underlying TIS and its long-term implications is crucial for improving therapeutic strategies and minimizing late adverse effects.

Emerging evidence suggests that TIS also affects genomic stability in surviving cells. Senescent cells exhibit increased Reactive Oxygen Species (ROS) production, mitochondrial dysfunction, and impaired DNA repair mechanisms. Persistent ROS can induce Deoxyribonucleic Acid (DNA) damage in adjacent cells, while dysfunctional mitochondria contribute to metabolic alterations that favor oncogenic transformation. Additionally, epigenetic changes, including chromatin remodeling and histone modifications, stabilize the senescent phenotype but may inadvertently deregulate oncogene and tumor suppressor gene expression. Together, these processes establish a microenvironment where cells with accumulated genomic lesions may escape growth arrest, leading to therapy-related secondary malignancies.

Clinical studies support the link between therapy-induced senescence and secondary cancer risk. Long-term survivors of chemotherapy or radiotherapy for primary malignancies such as Hodgkin lymphoma, breast cancer, or pediatric leukemias exhibit increased incidence of secondary malignancies, including therapy-related myeloid neoplasms and solid tumors. While multiple mechanisms contribute to secondary cancer development-including direct DNA mutagenesis-TIS and SASP-mediated tissue remodeling provide a complementary explanation for the late-onset emergence of secondary neoplasms. Moreover, the magnitude of TIS and SASP secretion may vary depending on the type, dose, and schedule of therapy, as well as individual patient factors, including genetic predisposition and immune competence.

The immune system also plays a critical role in regulating TIS and its consequences. Senescent cells are typically recognized and cleared by innate immune cells, including natural killer cells, macrophages, and cytotoxic T lymphocytes. Efficient immune surveillance reduces SASP accumulation and tissue damage, whereas impaired clearance leads to persistence of senescent cells and chronic inflammation. Immunosenescence, therapy-induced immunosuppression, or age-related immune decline may exacerbate the pro-tumorigenic effects of TIS. Strategies to boost immune-mediated clearance of senescent cells, such as immune checkpoint modulation or adoptive cell therapy, are being explored as potential interventions to reduce secondary malignancy risk.

Advances in molecular profiling and single-cell analysis provide mechanistic insights into TIS heterogeneity. Not all senescent cells exhibit identical SASP profiles, and tumor stromal senescent cells may have distinct effects on tissue homeostasis. Single-cell transcriptomics, proteomics, and metabolomics enable the characterization of senescence-associated phenotypes, identification of pro-tumorigenic subsets, and discovery of novel therapeutic targets. Integration of these high-dimensional data with clinical outcomes could inform patient-specific interventions to mitigate secondary cancer risk while preserving the tumor-suppressive benefits of TIS.

CONCLUSION

Therapy-induced senescence is a complex cellular response that serves as a double-edged sword in cancer treatment. While TIS contributes to tumor suppression through permanent growth arrest, the associated SASP, genomic instability, and impaired tissue homeostasis can promote secondary malignancy development. Understanding the molecular mechanisms

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underlying TIS, including DNA damage response, ROS generation, mitochondrial dysfunction, epigenetic remodeling, and immune interactions, is essential for developing strategies to minimize long-term adverse effects.

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