Cancer Cell Fusion

Subjects: Biochemistry & Molecular Biology

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"A major challenge in treating cancer is posed by intratumor heterogeneity, with different sub-populations of cancer cells within the same tumor exhibiting therapy resistance through different biological processes. These include therapy-induced dormancy, apoptosis reversal (anastasis), and cell fusion. Unfortunately, such responses are often overlooked or misinterpreted as “death” in commonly used preclinical assays.This entry highlights the dark side of cell fusion in metastasis and therapy resistance of solid tumors."

Keywords: Cancer therapy ; cell fusion ; dormancy ; colony formation assay ; high-throughput assays.

1. Introduction

"Cancer cell fusion has emerged as a fundamental non-genetic mechanism that contributes to intratumor heterogeneity, resulting in tumor progression (invasive growth and metastasis) and therapy resistance".

2. Role of Cancer Cell Fusion in Metastasis and Therapy Resistance

"As recently pointed out by different authors[1][2][3][4], the potential role of fusion between cancer cells and motile leukocytes in promoting metastasis was proposed by the German pathologist Prof. Otto Aichel nearly a century ago. This intriguing hypothesis remained controversial during the 20th century when the somatic mutation theory of carcinogenesis was the dominant force driving cancer research. In the past decade, however, a significant number of reports have underscored the importance of cell fusion in tumor progression and therapy resistance in a wide range of malignancies (e.g., [1][2][3][4][5][6][7][8][9][10]). In a recent study reported by Gast and associates [9], for example, cancer cell-leukocyte hybrids were detected in peripheral blood of cancer patients, and the numbers of such hybrids in the patient’s blood correlated with disease stage and predicted overall survival. In addition, cancer cells obtained from metastatic tumors of women who years earlier had received a bone marrow transplant from a male donor were shown to carry a Y chromosome, indicating that metastasis originated from fusion between patient cancer cells and donor bone marrow cells[9]. In that study, the Y chromosome was present in metastatic cancers of all patients that were examined, which involved women with kidney, head and neck, lung, and pancreatic cancers[9].

As noted by those authors, the presence of tumor cells with acquired leukocyte phenotypes “supports a cell fusion mechanism in the propagation of intratumor heterogeneity, introduces a functionally significant aspect of tumor progression and evolution, identifies an unappreciated circulating hybrid cell population, and uncovers a new area of tumor cell biology”[9].

In addition to cancer cell–leukocyte fusion, fusion between cancer and cancer cells[11][12][13], between cancer and stem cells[14][15][16][17], and between cancer and stromal cells[18][19] are also known to promote tumor progression/therapy resistance. Fusion between different cell types within a solid tumor is perhaps not unexpected given that “a tumor tissue resembles chronically inflamed tissue, that chronically inflamed tumor tissue efficiently recruits macrophages, mesenchymal stem cells and hematopoietic stem/progenitor cells, that chronic inflammatory conditions are a positive trigger for cell fusion”[10].

Fused cells undergo heterokaryon-to-synkaryon transition, reflecting nuclear fusion, which results in a loss and/or re-sorting of chromosomes in a random manner[10]. These events give rise to unique hybrid cells in which the degree of aneuploidy/genomic instability is further enhanced during subsequent rounds of cell division. Fused cells and most (but not all)[20]of their hybrid descendants exhibit increased resistance to anticancer agents relative to their unfused parental cells when assessed in vitro (e.g., using flow cytometric approaches)[20]and in tumor growth studies with live animals[12][20].

Fusions can occur between several cells simultaneously within a tumor, causing the formation of PGCCs, which underlie therapy resistance, metastasis, and disease recurrence as outlined above (Section 3.1). In human glioblastoma cell cultures, for example, the formation of PGCCs following exposure to ionizing radiation has been reported to be largely associated with homotypic cell fusion[11]."

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