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Letter to the editor

Assessing the role of cell fusion in cancer metastasis

Introduction

Metastasis is the leading cause (90%) for mortality in cancer [1]. Metastasis in an epithelial malignancy (carcinoma), can be divided into 2 major steps. The first step involves epithelial-mesenchymal transition (EMT) wherein the carcinoma loses its epithelial properties (cell to cell adhesion) and acquires mesenchymal properties (migration) allowing the cancer cells to detach and migrate away from a primary tumor. The second stage involves mesenchymal-epithelial transition (MET) wherein the migrating tumor cells re-acquire the epithelial properties and establish a metastatic deposit on a distant site [2]. As EMT and MET are major determinants of metastasis it is essential to understand factors determining these transitions. The present manuscript reviews the potential role of cell fusion in metastasis including EMT and MET.

Cancer cell fusion

Cell fusion can be a part of both physiological (fertilization) and pathological (cancer) event [2–4]. In cancer, cell fusion can be either between the cancer cells (homo-fusion) or between the cancer cells and the normal cells (hetero-fusion). Studies have shown that the resulting hybrid cells exhibit properties of both the parent cells [5–9]. Thus, if a cancer cell fuses with another cancer cells, the resulting hybrid cells may have properties of both the cancer cells which often imparts more aggressiveness including metastatic potential and ability to resist treatment [2,5,8,9]. In contrary, if the cancer cell fuses with a normal cell with a functioning tumor suppressor gene, and the resulting hybrid cell retains the tumor suppressor gene then it may not exhibit carcinogenic property [2]. Thus, the behavior of the hybrid cell depends on the characteristics of the parent cells.

Role of cancer cell fusion in metastasis

EMT: Based on the premise of hybrid cells expressing properties of both parent cells, when an epithelial cancer cell fuses with a mesenchymal cell in the tumor microenvironment, the resulting hybrid cancer cells would have both epithelial and mesenchymal properties. Thus, such a hybrid cancer cell in a predominant mesenchymal tumor microenvironment could modify its expression levels, such that its epithelial properties including cell to cell adhesion are decreased and mesenchymal properties including migration are enhanced [2].

MET: When the migrating cancer hybrid cell reaches a distant site, the local epithelial microenvironment could induce the cancer cells into enhancing its epithelial characteristics allowing the cancer cell to proliferate and establish a metastatic deposit [2].

Polyploid giant cancer cells

Cell fusion doesn't necessarily mean one cell fusing with another to form a hybrid cell. The fusion can occur between several cells leading to the formation of polyploid giant cells. As cancer microenvironment (hypoxic and acidic) suits cell fusion, the occurrence of polyploid giant cancer cells (PGCCs) [Fig. 1] are not uncommon [2]. PGCCs are more aggressive than the parent cancer cells. Studies have shown that when a

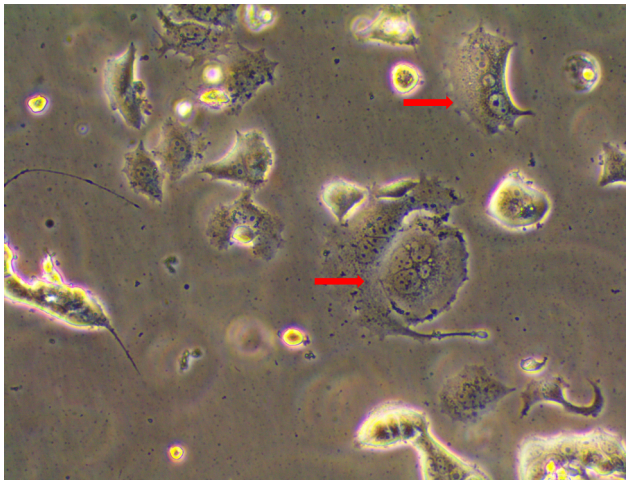

Fig. 1. Giant cancer cells (arrows) resulting from fusion of several MCF7 (breast cancer cell line) cells.

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cancer cell resistant to drug A is fused with cancer resistant to drug B, the resulting cancer hybrid cell can be resistant to both drug A and drug B and have shown resistance to other drugs to which neither parent cells are resistant [2,9]. Thus, as more cancer cells fuse among themselves, the chances are greater than the resulting hybrid cell will be more aggressive and treatment-resistant. In addition to this, PGCCs have shown to exhibit stem cell-like properties and are proposed to be a potential source for cancer stem cells [10]. In metastasis, apart from acquiring mesenchymal properties from cell fusion, the hybrid cell should have the ability to survive the distant migration. Given the high tumorigenic, stem cell-like and chemo-resistant properties, a PGCCs fused with a mesenchymal cell has a greater chance of successfully migrating and establishing itself in a distant site. Thus, further studies must assess if the presence of PGCCs has any bearing on the overall tumor behavior especially pertaining to its metastatic potential.

Implications: As cell fusion (homo/hetero-fusion) is a common event in cancer, the properties of the resulting hybrid cells may well determine the overall tumor behavior. Thus, future studies must explore the molecular factors and pathways involved in cancer cell fusion which could aid us in strategizing cell fusion based treatment strategies such as:

(I) Inhibition of homo cancer cell fusion to prevent PGCCs formation.
(II) Inhibition of hetero cancer cell fusion with the tumor-microenvironment stromal cell to prevent acquirement of mesenchymal properties
(III) Introduction of healthy cells with functioning tumor suppressor gene and stimulating its fusion with cancer cells.

Conflict of interest

None declared.

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