To cite this version:


HAL Id: inserm-01855880
https://www.hal.inserm.fr/inserm-01855880
Submitted on 8 Aug 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Tunneling Nanotubes (TNTs): Intratumoral Cell-to-Cell Communication and Mitochondria Trafficking Through Connections by Tunneling Nanotubes—Effects on Cell Metabolism and Response to Therapy

Marie-Luce Vignais and Jean Nakhle, IRMB, INSERM, CNRS, University of Montpellier, Montpellier, France
Emmanuel Griessinger, INSERM, C3M, Nice, France; University of Nice Sophia, Nice, France
© 2017 Elsevier Inc. All rights reserved.

Intercellular Connections in Tumors

1 General Features of TNT-Dependent Cell-to-Cell Exchanges

2 Cell Types Involved in TNT Connections

3 Cargos Transported Between TNT-Connected Cells

3 Mitochondria

3 Other Cargos

6 Mechanisms of TNT and Gap Junction-Dependent Cell-to-Cell Exchanges

6 Signals That Regulate TNT Formation and Cargo Trafficking

7 TNT/Gap Junction-Dependent Connections in Cancer

8 Prospective View

8 References

10 Further Reading

Intercellular Connections in Tumors

Solid tumors and hematological malignancies are considerably heterogeneous tissues. This heterogeneity comes from the tumor cells themselves that include cancer stem cells (CSCs), believed to be responsible for tumor progression and recurrence following therapy, and cancer cells stratified at different stages of differentiation. Neoplastic tissues also include non-cancer cells. These comprise residing mesenchymal, epithelial and endothelial cells, as well as cells recruited by the tumor such as immune cells and mesenchymal stem cells (MSCs). Importantly, although non-cancerous, these cells nonetheless often present a modified and abnormal phenotype due to their location in the tumor microenvironment and consequently favor tumor progression, metastasis and resistance of the cancer cells to therapy.

Cell communication within the tumor, amongst cancer cells themselves and between cancer and non-cancer cells is now fully acknowledged as widely used by the tumor to grow and circumvent therapeutic treatments. In the last decades, this intercellular communication was believed to heavily rely on secreted cytokines/chemokines, metabolites and extracellular vesicles. In the past few years, a new means of cell-to-cell communication that uses tunneling nanotubes (TNTs) was shown to enable cells to connect to far-off cells and to transfer them biological cargos, ranging from ions to whole organelles, as it will be detailed in this chapter. This donation is qualified horizontal, to distinguish it from the vertical donation from a parental cell to its offspring during mitosis. The number of scientific publications describing this TNT-mediated new mode of communication between cells, including cancer cells, steadily increased since 2004, when they were initially described (Fig. 1). Importantly, TNTs involving cancer cells were also observed in situ, in patient resected solid tumors from both malignant pleural mesothelioma and lung adenocarcinoma, demonstrating their relevance in the cancer pathology.

The occurrence of TNTs in tumors and the ensuing intercellular trafficking are now bringing about a radical turmoil in the current paradigm of the intercellular communications that take place in tumors as TNTs guide and allow the dynamic fluxes of biological cargos, notably mitochondria, that are literally passed from the cytoplasm of the donor cell to that of the recipient cell. This TNT-mediated trafficking occurs from cells of the microenvironment to the cancer cells, modifying the functional properties and response to therapy of the tumor cells. It also occurs in the reverse direction, from the cancer cells to non-cancer cells of the tumor microenvironment, likely contributing to the observed changes in phenotype of these normal cells that ultimately further contribute to tumor progression and resistance to therapy.

General Features of TNT-Dependent Cell-to-Cell Exchanges

TNTs are long tubular structures, with diameters ranging from 50 and 1500 nm and lengths that can span several tens to hundreds of microns. The most important feature of TNTs is definitely the fact that they allow cytoplasm continuity between the connected cells and consequently enable the transport of cellular components between these cells. The transported cargos include a whole panel of cellular components, from ions, miRNAs, proteins and virus to whole organelles like lysosomes and mitochondria, as schematized in Fig. 2.