



# **Tunneling Nanotubes (TNTs): Intratumoral Cell-to-Cell Communication and Mitochondria Trafficking Through Connections by Tunneling Nanotubes-Effects on Cell Metabolism and Response to Therapy**

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## **► To cite this version:**

Marie-Luce Vignais, Jean Nakhle, Emmanuel Griessinger. Tunneling Nanotubes (TNTs): Intratumoral Cell-to-Cell Communication and Mitochondria Trafficking Through Connections by Tunneling Nanotubes-Effects on Cell Metabolism and Response to Therapy. Encyclopedia of Cancer 3rd edition, 2019, 10.1016/B978-0-12-801238-3.65215-7 . inserm-01855880

**HAL Id: inserm-01855880**

**<https://inserm.hal.science/inserm-01855880>**

Submitted on 8 Aug 2018

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# Tunneling Nanotubes (TNTs): Intratumoral Cell-to-Cell Communication and Mitochondria Trafficking Through Connections by Tunneling Nanotubes—Effects on Cell Metabolism and Response to Therapy

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## 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.