Received: 13 December 2018 | Revised: 24 April 2019 | Accepted: 11 September 2019

DOI: 10.1002/cnr2.1228

EDITORIAL

WILEY Cancer Reports

Role of cell-to-cell communication in cancer: New features, insights, and directions

Abstract

The current special issue entitled "Role of tunneling nanotubes (TNTs) in carcinogenesis" was designed to discuss the role of cell-to-cell communication, especially TNTs, in cancer pathogenesis. In addition, we discuss the exploitation of TNTs as a potential therapeutic target to prevent and reduce cancer incidence. It is accepted that cell-to-cell communication is essential for the development of multicellular systems, and it is coordinated by soluble factors, associated membrane proteins, exosomes, gap junction channels, and TNTs. An old belief in the cancer field is that cancer cells are "disconnected" from healthy cells, resulting in loss of cell-to-cell communication and neighbor control. However, recent data obtained from different kind of tumors indicate that TNTs and others forms of communication (exosomes and localized cell-to-cell communication) are highly expressed and functional during tumor development . In physiological conditions, TNTs are expressed by few cells, and their main function is to coordinate long-distance signaling. However, upon carcinogenesis, TNTs proliferate and provide an alternative route of communication to enable the transfer of several signaling molecules and organelles to spread disease and toxicity. We propose that TNTs and their cargo are an attractive therapeutic target to reduce or prevent cancer development. All these unique aspects of cell-to-cell diffusion and organelle sharing will be discussed in this special issue.

1 | INTRODUCTION

As indicated by the National Cancer Institute (NCI) in 2018-2019, an estimated 1.7 million new cases of cancer were diagnosed, and around 600 000 people will die from the disease in this period. The most common cancers in the US are breast, lung, bronchus, prostate, colon and rectum, melanoma, bladder, pancreatic, and liver. Even though several of these cancers have a good rate of cure and survival, some still have a poor prognosis and limited treatment options—as is the case with pancreatic/colon-rectal cancer and glioblastoma—despite increasing surveillance (https://www.cancer.gov/about-cancer/understanding/statistics).

A simplistic summary of cancer development is that carcinogenesis initiates as a result of the sustained proliferative stage; evasion of growth suppressors; resistance to cell death becoming stem cell–like; the promotion of angiogenesis; a metabolic shift and environment adaptation; cell migration or metastasis; and the regulation of the immune response to promote carcinogenesis. The overall mechanism is extremely complex, but it is accepted that tumor initiation involves genetic mutation, epigenetic changes, environmental factors, and immune components. However, how do tumor cells survive immune surveillance? How do tumors become heterogeneous? and how do tumors adapt to treatments? All these questions are poorly understood. We propose that TNTs play a key role in all these cancer-related mechanisms, and some of these novel ideas will be discussed in this special issue.

After tumor detection, several treatments have been developed to combat it, including radiation, chemotherapeutics to prevent reliable DNA replication, hypo-methylation agents, targeting signaling molecules, and finally busting the immune system.[1-4] However, the clinical identification of tumors, classification, and selection of treatment is still a major area of investigation. The latest advances in these areas are discussed by Dr. Krishna Bhat (M.D. Anderson, Houston, Texas) as he recently described.[5,6]

In this special issue, we provide a collection of provocative articles discussing the role of TNTs in the context of tumor-microenvironment communication and promising potential therapeutic approaches. Drs. Lou, Eugenin, Cox, and Osswald will discuss the potential therapeutic approaches that could provide a high reward for treating some of the aggressive cancers with low prognostic. Thus, the TNT field is exciting and on the rise.

Cell-to-cell communication is essential for a healthy microenvironment, as well as a tumorigenic one. For a long time, most research supported that tumor cells were isolated from the environment and that this lack of cell-to-cell communication contributed to compromised tissue homeostasis and promoted tumor development and growth. However, several new studies indicate that cell-to-cell communication was essential in shaping the nature of the microenvironment to create the tumor niche.[7-9] Due to the complexity of the generation of the tumor niche, we will focus on the role of TNTs in breast and glioblastoma pathogenesis as well as new methods to use OMICs data to find novel therapeutic targets to reduce or prevent the devastating

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consequences of deadly cancers. Dr. Prideaux will discuss new approaches using imaging mass spectrometry to examine the different microenvironments or biomarkers of disease present within a tumor and the tools available to understand cancer pathogenesis. Dr. Valdebenito S. will focus on the heterogeneity of the tumor and the potential role of TNTs in tumor development and treatment resistance. Furthermore, Drs. Valdebenito J. and Medina will explain novel approaches to using large databases to learn and identify new biomarkers of disease including approaches to assess the role of TNTs and its cargo in cancer pathogenesis.

2 | TUNNELING NANOTUBES (TNTs): A KEY FORM OF CELL-TO-CELL COMMUNICATION IN CANCER PATHOGENESIS

TNT's and gap junctions (GJ) are the only two communication systems that allow a direct exchange of cytoplasmic factors between connected cells. Both systems participate in critical biological processes, including cell-to-cell coordination of development, signaling, and immune response, but are also important in the pathogenesis of several diseases, including HIV and cancer. In this special issue, we discuss some of the similarities and distinct features of GJ and TNTs in cancer development. Recently, we have identified that some types of TNTs have GJ and uHC at the tip of the process, suggesting that at least two different types of TNTs exist: an open-ended type and a process with GJ and uHC at the end of it. In the open-ended TNTs, lysosomes, vesicles, and mitochrondria can be transferred between connected cells to spread disease. Both of these process types will be discussed in all the subsequent chapters especially in Dr. Osswald and Dr. Geiger's chapters.

TNTs have only been described relatively recently (the early 2000s), maybe due to their small diameters and fragility upon fixation. TNTs are long membrane extensions that allow the exchange of several small molecules, vesicles, and mitochondria, as well as several pathogenic components including bacteria, viruses, and pathogenic proteins such as prions, and aggregated proteins such as tau or beta amyeloid. They also allow the exchange of genetic and metabolic signatures that promote carcinogenesis. TNTs are around 50 to 200 nm in diameter and several μm in length with no contact to the substrate. Works of several laboratories demonstrated that TNTs are positive for f-actin, myosin Va, and myosin X but are tubulin negative.[10-14] However, a specific biomarker for TNTs is still necessary to identify these processes in vitro and in vivo. Some of the new potential TNTs biomarkers are discussed in several of the chapters.

3 | TNT-LIKE STRUCTURES IN VIVO

Currently, most of the data available about TNTs were obtained in vitro. However, whether these processes are present in vivo is still under debate, mainly because the definition and particular markers to identify TNTs is still under active investigation. In this special issue, several new examples of in vivo communication will be discussed.

Currently, in vivo, several suggestive publications show TNT-like structures in MHC class II dendritic cells in the corneal stroma,[15] non-neural ectoderm cells in the midbrain,[16] trophectoderm cells in the neural crest,[17] epiblast cells in the blastula,[18] and the ectoderm.[19] Also, several groups have suggested that neuronal processes may be similar to TNTs. However, we will exclude this possibility from this review, because dendrites are a clear formation, transport, and stability and lack many components of TNTs.

Probably one of the best examples of TNTs in vivo has been described in flies. Only recently has the role of TNTs or cytoneme been well described by several groups, indicating their critical role of these processes in signaling and delivery of developmental proteins such as DPP, fibroblast growth factor (FGF), Hedgehog, Wingless (in flies), Sonic Hedgehog (chick limbs), and wnt proteins (in developing zebrafish) directly into sites of cell-to-cell contact without dilution of these factors into the extracellular space.[20-25] TNTs are a changing paradigm in the area because it was assumed that most of these proteins were released into extracellular space. Roy et al. describe that DPP and FGF signaling is required for signal-producing wing disc cells and that several of the genes activated by these factors are required for TNT (cytoneme) or synapse formation.[26-28] It appears as though most of the evidence indicates that other factors important in the development of flies are TNT-mediated, such as fibroblast growth factor branchless,[29] Dpp,[25,27] EGF, Hh,[21] SHh,[30] and Notch.[26-28,31] Most of the factors are also present in humans. Thus, it may be possible to extrapolate some of these data into human development and disease. In this special issue, several examples will be discussed in several kinds of cancers.

Only recently by Dr. Osswald, using an animal model of glioblastoma, described TNT-like structures in vivo that has been associated with brain colonization, growth, and severity of GBM disease. This communication identified several potential mediators of TNT formation such as tweety-homolog 1 (Ttyh1) and GAP43 as key molecules involved in TNT formation.[32-34] However, the mechanisms of formation, stability, transport, and collapse of TNTs are unknown. New experimental approaches to revealing the pathways are involved in TNT biology, as discussed in the current special topic, using large data bases, artificial intelligence (AI) and machine learning (see manuscript byDrs. Valdebenito J. and Medina).

4 | ROLE OF TNTs IN CANCER PATHOGENESIS

Most of the data involving TNTs or tumor microtubes (TMs) in GB are generated in two laboratories, Dr. Osswald (University of Heidelberg, Germany) and Dr. Lou (University of Minnesota, USA). Both groups are contributing to this special issue. In breast cancer (Dr. Cox will provide an overview of breast cancer and TNTs), TNTs are highly functional and correlate with tumor aggressiveness.[35] Also, our unpublished data indicate that radiation and TMZ treatment induces the formation of TNTs, maybe helping the tumor to have a better adaption to treatment. This point is concerning as it involves a mechanism of

tumor protection against treatment. Furthermore, the examination of the transported materials between connected cells indicates that TNTs are an efficient mechanism of transport for DNA repair enzymes. Thus, it is essential to learn the consequences of TNTs in cancer progression and also its resistance to treatment.

Overall, the field of TNTs is rapidly growing, and more laboratories see them in vivo and in vitro. In addition, the role of TNTs is clearly defined under pathological conditions, but the role of TNTs in development and healthy conditions is unknown. This exciting topic has resulted in several cutting-edge discoveries and publications enhancing the interest and impact of TNT in cancer and infectious diseases. We thank all the contributors to this special issue as well as the reviewers for their supportive and constructive comments.

ACKNOWLEDGMENTS

This work was funded by the National Institute of Mental Health grant (MH096625), the National Institute of Neurological Disorders and Stroke (NS105584), and U.T.M.B. internal funding (to E.A.E.).

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTION

The author had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and performed all the *conceptualization*, *methodology*, *investigation*, *formal analysis*, *resources*, *writing - original draft*, *writing - review & editing*, *visualization*, *supervision*, *funding acquisition*.

Keywords

breast, carcinogenesis, glioblastoma, glioma, pancreatic

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REFERENCES

1. Greil R, Hutterer E, Hartmann TN, Pleyer L. Reactivation of dormant anti-tumor immunity—a clinical perspective of therapeutic immune checkpoint modulation. *Cell Commun Signal*. 2017;15(1):5, 1-16.
2. Wessler S, Aberger F, Hartmann TN. The sound of tumor cell-microenvironment communication—composed by the Cancer Cluster Salzburg research network. *Cell Commun Signal*. 2017;15(1):20, 1-2.
3. Wessler S, Krisch LM, Elmer DP, Aberger F. From inflammation to gastric cancer—the importance of Hedgehog/GLI signaling in *Helicobacter pylori*-induced chronic inflammatory and neoplastic diseases. *Cell Commun Signal*. 2017;15(1):15, 1-13.
4. Visvanathan K, Fackler MS, Zhang Z, et al. Monitoring of serum DNA methylation as an early independent marker of response and survival in metastatic breast cancer: TBCRC 005 Prospective Biomarker Study. *J Clin Oncol*. 2017;35(7):751-758.
5. Balasubramaniyan V, Bhat KP. Targeting MIR155HG in glioma: a novel approach. *Neuro Oncol*. 2017;19(9):1152-1153.
6. Audia A, Conroy S, Glass R, Bhat KPL. The impact of the tumor microenvironment on the properties of glioma stem-like cells. *Front Oncol*. 2017;7:143.
7. Hanahan D, Coussens LM. Accessories to the crime: functions of cells recruited to the tumor microenvironment. *Cancer Cell*. 2012;21(3):309-322.
8. Lindau D, Gielen P, Kroesen M, Wesseling P, Adema GJ. The immunosuppressive tumour network: myeloid-derived suppressor cells, regulatory T cells and natural killer T cells. *Immunology*. 2013;138(2):105-115.
9. Quail DF, Siegers GM, Jewer M, Postovit LM. Nodal signalling in embryogenesis and tumourigenesis. *Int J Biochem Cell Biol*. 2013;45(4):885-898.
10. Las G, Shirihai OS. Miro1: new wheels for transferring mitochondria. *EMBO J*. 2014;33(9):939-941.
11. Austefjord MW, Gerdes HH, Wang X. Tunneling nanotubes: diversity in morphology and structure. *Commun Integr Biol*. 2014;7(1):e27934.
12. Schiller C, Diakopoulos KN, Rohwedder I, et al. LST1 promotes the assembly of a molecular machinery responsible for tunneling nanotube formation. *J Cell Sci*. 2013;126(Pt 3):767-777.
13. Gerdes HH, Rustom A, Wang X. Tunneling nanotubes, an emerging intercellular communication route in development. *Mech Dev*. 2013;130(6-8):381-387.
14. Abounit S, Zurzolo C. Wiring through tunneling nanotubes—from electrical signals to organelle transfer. *J Cell Sci*. 2012;125(Pt 5):1089-1098.
15. Chinnery HR, Pearlman E, McMenamin PG. Cutting edge: membrane nanotubes in vivo: a feature of MHC class II+ cells in the mouse cornea. *J Immunol*. 2008;180(9):5779-5783.
16. Pyrgaki C, Trainor P, Hadjantonakis AK, Niswander L. Dynamic imaging of mammalian neural tube closure. *Dev Biol*. 2010;344(2):941-947.
17. Teddy JM, Kulesa PM. In vivo evidence for short- and long-range cell communication in cranial neural crest cells. *Development*. 2004;131(24):6141-6151.
18. Caneparo L, Pantazis P, Dempsey W, Fraser SE. Intercellular bridges in vertebrate gastrulation. *PLoS ONE*. 2011;6(5):e20230.
19. Miller J, Fraser SE, McClay D. Dynamics of thin filopodia during sea urchin gastrulation. *Development*. 1995;121(8):2501-2511.
20. Bilioni A, Sánchez-Hernández D, Callejo A, et al. Balancing Hedgehog, a retention and release equilibrium given by Dally, Ihog. *Boi and shifted/DmWif Dev Biol*. 2013;376(2):198-212.
21. Bischoff M, Gradilla AC, Seijo I, et al. Cytonemes are required for the establishment of a normal Hedgehog morphogen gradient in *Drosophila* epithelia. *Nat Cell Biol*. 2013;15(11):1269-1281.
22. Gradilla AC, González E, Seijo I, et al. Exosomes as Hedgehog carriers in cytoneme-mediated transport and secretion. *Nat Commun*. 2014;5(1):5649, 1-13.
23. Kornberg TB. The contrasting roles of primary cilia and cytonemes in Hh signaling. *Dev Biol*. 2014;394(1):1-5.

24. Rojas-Rios P, Guerrero I, Gonzalez-Reyes A. Cytoneme-mediated delivery of hedgehog regulates the expression of bone morphogenetic proteins to maintain germline stem cells in *Drosophila*. *PLoS Biol*. 2012;10(4):e1001298.

25. Roy S, Hsiung F, Kornberg TB. Specificity of *Drosophila* cytonemes for distinct signaling pathways. *Science*. 2011;332(6027):354-358.

26. Kornberg TB, Roy S. Cytonemes as specialized signaling filopodia. *Development*. 2014;141(4):729-736.

27. Roy S, Huang H, Liu S, Kornberg TB. Cytoneme-mediated contact-dependent transport of the *Drosophila* decapentaplegic signaling protein. *Science*. 2014;343(6173):1244624.

28. Roy S, Kornberg TB. Paracrine signaling mediated at cell-cell contacts. *Bioessays*. 2015;37(1):25-33.

29. Sato M, Kornberg TB. FGF is an essential mitogen and chemoattractant for the air sacs of the drosophila tracheal system. *Dev Cell*. 2002;3(2):195-207.

30. Sanders TA, Llagostera E, Barna M. Specialized filopodia direct long-range transport of SHH during vertebrate tissue patterning. *Nature*. 2013;497(7451):628-632.

31. Callejo A, Bilioni A, Mollica E, et al. Dispatched mediates Hedgehog basolateral release to form the long-range morphogenetic gradient in the *Drosophila* wing disk epithelium. *Proc Natl Acad Sci U S A*. 2011;108(31):12591-12598.

32. Winkler F, Wick W. Harmful networks in the brain and beyond. *Science*. 2018;359(6380):1100-1101.

33. Winkler F, Osswald M, Wick W. Anti-angiogenics: their role in the treatment of glioblastoma. *Oncol Res Treat*. 2018;41(4):181-186.

34. Jung E, Osswald M, Blaes J, et al. Tweety-Homolog 1 drives brain colonization of gliomas. *J Neurosci*. 2017;37(29):6837-6850.

35. Osswald M, Jung E, Sahm F, et al. Brain tumour cells interconnect to a functional and resistant network. *Nature*. 2015;528(7580):93-98.