

REVIEW ARTICLE

Cell-to-cell contact-mediated regulation of tumor behavior in the tumor microenvironment

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Abstract

Tumor growth and progression are complex processes mediated by mutual interactions between cancer cells and their surrounding stroma that include diverse cell types and acellular components, which form the tumor microenvironment. In this environment, direct intercellular communications play important roles in the regulation of the biological behaviors of tumors. However, the underlying molecular mechanisms are insufficiently defined. We used an in vitro coculture system to identify genes that were specifically expressed at higher levels in cancer cells associated with stromal cells. Major examples included epithelial membrane protein 1 (EMP1) and stomatin, which positively and negatively regulate tumor progression, respectively. EMP1 promotes tumor cell migration and metastasis via activation of the small GTPase Rac1, while stomatin strongly suppresses cell proliferation and induces apoptosis of cancer cells via inhibition of Akt signaling. Here we highlight important aspects of EMP1, stomatin, and their family members in cancer biology. Furthermore, we consider the molecules that participate in intercellular communications and signaling transduction between cancer cells and stromal cells, which may affect the phenotypes of cancer cells in the tumor microenvironment.

KEYWORDS

intercellular communication, signal transduction, stroma, tumor invasion, tumor microenvironment

1 | INTRODUCTION

Tumor growth and progression are complex processes that involve interactions between cancer cells and their surrounding stroma. These interactions are required for the formation of the so-called tumor microenvironment, which includes numerous types of cells, such as fibroblasts and immune cells, as well as acellular components such as the extracellular matrix and associated soluble factors.¹

These cells and components of the tumor microenvironment differ according to type, developmental stage and location of tumors, and function in a context-dependent manner.²

The outcomes of the association between cancer cells and stroma lead to positive or negative regulation of tumor progression.³ When cancer cells appear during the early stage of tumor development, the surrounding stroma is mainly composed of normal cells that preferentially suppress tumor growth. However, during tumor

Abbreviations: EMP1, epithelial membrane protein 1; HSP90, heat shock protein 90; PD-L1, programmed cell death-ligand 1; PDPK1, phosphoinositide-dependent protein kinase 1; PrS, primary human prostate stroma; SPFH, stomatin, prohibitin, flotillin, and HflK/C; TM, tumor microtube; TNT, tunneling nanotube.

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progression, a subpopulation of cancer cells resist stroma-mediated suppression, and begin to reprogram and remodel the surrounding stroma to support further tumor progression.⁴ This transition induces tumor progressive activities of stromal cells through epigenetic modifications and locally acting signals, which serves as a critical driver of malignancy.⁵ Moreover, the tumor microenvironment exhibits spatiotemporally promotive or suppressive functions that contribute to tumor progression.⁶

Numerous studies have shown that classical paracrine and endocrine signaling via the secretion of soluble factors, including cytokines and growth factors, into the extracellular space contribute to the regulation of the tumor microenvironment to suppress or promote tumor progression.^{3,4,7} Furthermore, direct contact between cancer cells and stromal cells may crucially affect the biological behavior of cancer cells,⁸ although few studies focus on this process. Therefore, this review article highlights recent findings that illuminate how direct cell-to-cell contact and intercellular communication between cancer cells and stromal cells regulate the characteristics and behaviors of cancer cells during tumor progression.

2 | DIRECT CELL-TO-CELL CONTACT-INDUCED GENE EXPRESSION IN CANCER CELLS THROUGH THEIR ASSOCIATIONS WITH STROMAL CELLS

To determine how stromal cells regulate tumor behavior through direct cell-to-cell contact in the microenvironment, we have recently screened for genes that are upregulated in prostate cancer LNCaP cells when they directly associate with primary human prostate stroma (PrS) cells. For this purpose, we used an *in vitro* coculture system that specifically detects the effect of direct cell-to-cell contact by limiting the effects of soluble factors secreted from cancer cells and stromal cells.⁹ We identified 30 genes that were markedly upregulated in cocultured LNCaP cells, including epithelial membrane protein 1 (EMP1) and stomatin, which are associated with the plasma membrane. We have determined the functions of these proteins in cancer cells, particularly in prostate cancer cells.^{9,10} In this section, we introduce their detailed roles in cancer biology.

2.1 | EMP1

EMP1 is a member of the growth arrest-specific 3/peripheral myelin protein 22 kDa family, which belongs to the tetraspanin superfamily, and has been clarified to regulate membrane blebbing and inhibit spinal chondrocyte differentiation in cultured human cells.^{11,12} Among the members of this family, the amino acid sequences of EMP1, EMP2, and EMP3 are highly conserved and include four predicted transmembrane domains, two extracellular domains, and small intracellular domains.¹³ Each protein mediates tumor progression and suppression in a cancer type-dependent manner.¹⁴

As mentioned above, expression of EMP1 is upregulated in prostate cancer LNCaP cells cocultured with PrS cells, and increased EMP1 levels promote the progression of prostate cancer *in vitro* and *in vivo*.⁹ Gain of function of EMP1 in several types of cancer cells, including prostate, breast, and colorectal cancer cells, enhances their migration and invasiveness. LNCaP cells stably expressing EMP1 inoculated into the prostate glands of immunodeficient mice exhibit enhanced tumor metastasis into lymph nodes and lungs, compared with the control LNCaP cells. Primary tumors engrafted in the prostate gland similarly proliferate in control and EMP1-expressing LNCaP cells, suggesting that EMP1 does not affect tumor growth.

The intracellular domain of EMP1 directly binds to copine-III, which triggers an intracellular signaling cascade mediated by the protein tyrosine kinase Src and the Rac guanine nucleotide exchange factor Vav2 to activate the small GTPase Rac1, resulting in enhanced cell migration and invasiveness.⁹ EMP1 is uniformly distributed on the plasma membrane of cancer cells,⁹ while signaling molecules including Src and Rac1 are highly accumulated at the leading edge of migrating cells. One possible explanation for this different molecular accumulation is that growth factor signals, such as ErbB2 amplification,¹⁵ might support the recruitment of copine-III to the leading edge for inducing its interaction with EMP1 and subsequent activation of signaling molecules downstream of EMP1 and copine-III. In human prostate tumors, higher levels of EMP1 correlate with the degree of malignancy of prostate cancer. Together, these data support the conclusion that EMP1 promotes tumor metastasis by enhancing the movement of cancer cells (Figure 1). However, insufficient data are available to show how EMP1 expression is increased in cancer cells through direct association with stromal cells.

These findings have important clinical implications because they indicate that the development of a blocking antibody against EMP1 may inhibit metastasis. For example, inhibition of EMP2, which has pro-metastatic functions in certain cancers, by a recombinant anti-EMP2 bivalent antibody fragment reduces the aggressiveness of endometrial cancer.¹⁶ In our preliminary examination, the EMP1 antibody that we generated by using the epitope at the second extracellular loop of this protein showed an approximately 60% reduction of prostate cancer cell migration, which may contribute to inhibition of tumor metastasis. It is speculated that the binding of this antibody to EMP1 might change its conformation, followed by impairment of the EMP1-copine-III interaction. Further molecular structural study in the future would provide clear evidence for this speculation. In addition, small molecules and other agents that block the interaction between EMP1 and copine-III may serve as anti-metastatic cancer therapeutics.

In contrast with our findings, it has been reported that the levels of EMP1 are higher in normal tissues rather than prostate tumors, and that overexpression of EMP1 in PC3 prostate cancer cells decreases their migration and invasiveness.¹⁷ However, EMP1 is selected as one of the five novel predictive markers for poor outcomes of prostate cancer in African American men.¹⁸ Such a discrepancy in EMP1 function is also observed in breast cancer. For example, lobular carcinomas, highly malignant breast

FIGURE 1 EMP1-induced signal transduction promotes cancer metastasis. Interactions between cancer and stromal cells enhance EMP1 expression through an unidentified molecular mechanism, leading to activation of Rac1 to promote the migration of cancer cells and subsequent tumor invasion and metastasis

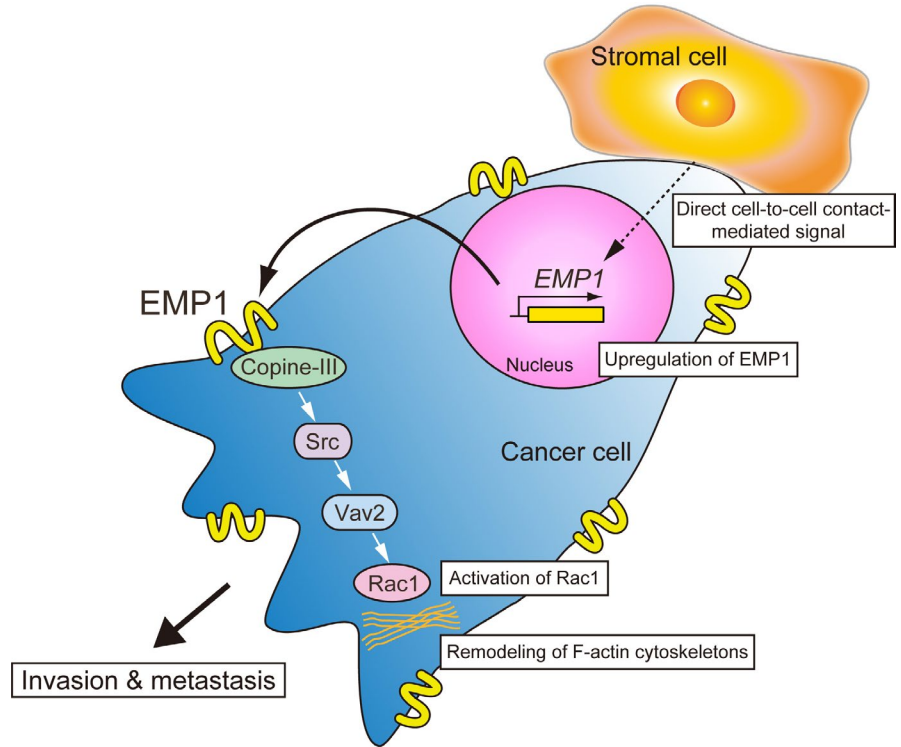
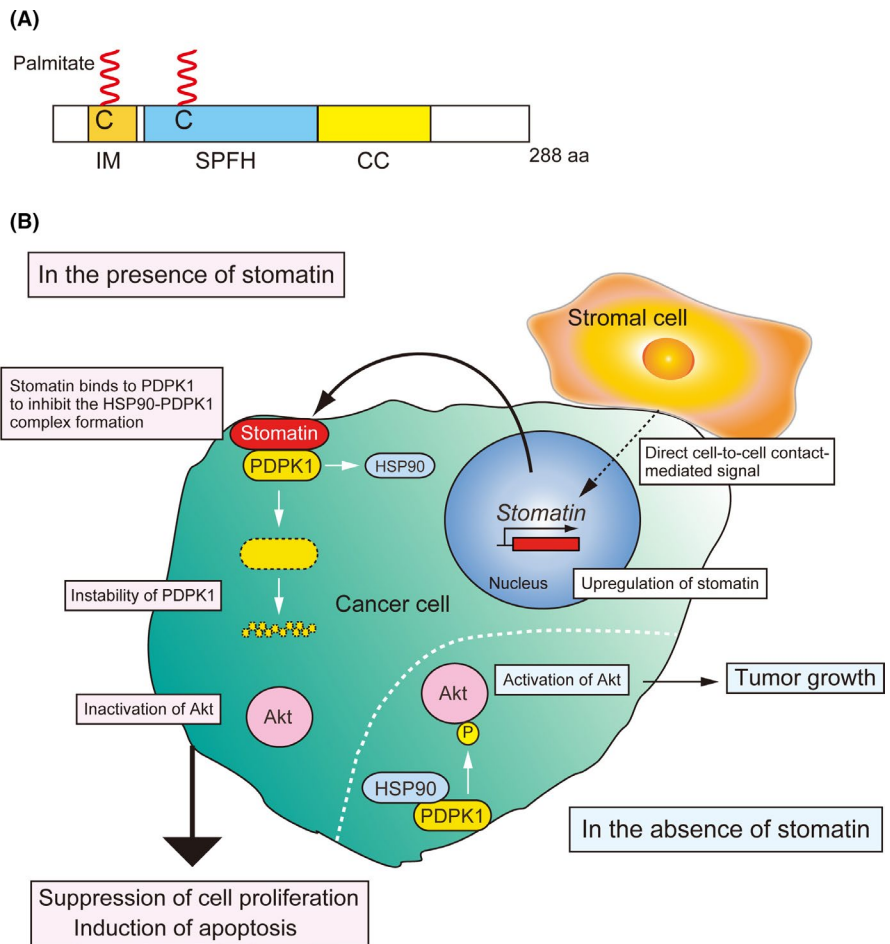


FIGURE 2 Stomatin-mediated inhibitory mechanism of tumor growth. A, Schematic models of stomatin. C, palmitoylated cysteine; CC, coiled-coil domain; IM, intramembrane domain; SPFH, stomatin, prohibitin, flotillin, and HflK/C domain. B, Increased stomatin expression induced by the cancer cell-stromal cell contact inhibits Akt activation by decreasing PDPK1 expression, followed by suppression of cancer cell proliferation and induction of apoptosis. In contrast, loss of stomatin facilitates tumor growth



tumors, express significantly higher levels of EMP1, compared with ductal carcinomas.^{19,20} In contrast, reduced expression of EMP1 is associated with shorter survival of patients with breast cancer.²¹ Furthermore, evidence indicates that EMP1 positively and negatively regulates tumor progression, including metastasis, depending on tumor type.^{17,22} Future studies are required to identify the factor(s) that switches between the tumor progressive and suppressive functions of EMP1.

2.2 | Stomatin

Stomatin is a member of the stomatin, prohibitin, flotillin, and HflK/C (SPFH) superfamily, which comprises stomatin, stomatin-like proteins, prohibitins, flotillin/reggie proteins, and HflK/C proteins. Members of the SPFH protein family, which are highly conserved among species, are expressed in red blood cells, fibroblasts, and cancer cells.²³ These proteins localize different intracellular compartments including membrane lipid rafts, and promote or inhibit diverse cellular functions, such as induction of endocytosis and reduction of protein synthesis.^{24,25} Stomatin was originally called “erythrocyte band 7.2b” and later given its name “stomatin,” because this protein is not expressed in patients with hereditary stomatocytosis, a form of hemolytic anemia.²⁶ However, different from humans, homozygous deletion of the gene encoding murine stomatin causes no obvious physiologically significant phenotype in mice.²⁷

Stomatin is a 31 kDa integral membrane protein possessing an intramembrane domain, two palmitoylated cysteines and a coiled-coil domain in addition to the conserved SPFH domain (Figure 2A), and mainly localizes on lipid rafts, to regulate the activities of several channels and transporters.²⁸⁻³⁰ Furthermore, stomatin is involved in the determination of cell morphology through binding to cortical actin in epithelial cells,^{31,32} and increased expression of stomatin promotes cell fusion.³³ Together, these findings provide compelling evidence that stomatin mediates events that occur on the plasma membrane. However, little information is known about the function of stomatin in cancer cells.

Similar to EMP1, LNCaP cells cocultured with PrS cells express significantly higher levels of stomatin.¹⁰ Induction of stomatin expression in LNCaP and PC3M cells, both of which do not express endogenous stomatin in the normal condition, strongly suppresses cell proliferation and induces apoptosis, leading to the inhibition of tumor growth.¹⁰ Stomatin-mediated tumor suppression is caused by the inhibition of the Akt signaling pathway, which is crucial for cell proliferation and survival.³⁴ Akt activation is mainly induced by phosphoinositide-dependent protein kinase 1 (PDPK1), and the stability of PDPK1 is maintained by its binding to heat shock protein 90 (HSP90).³⁵ Stomatin binds to PDPK1 and inhibits the formation of the PDPK1-HSP90 complex to inhibit PDPK1 expression. Conversely, loss of function of stomatin in prostate cancer 22Rv1 cells, which express a certain degree of stomatin endogenously on the plasma membrane, elevates Akt activation and enhances tumor growth.¹⁰

Clinically, stomatin levels are significantly decreased in human prostate cancers with high Gleason scores, and lower levels of stomatin are associated with increased recurrence of prostate cancer after surgery.¹⁰ These findings demonstrate the tumor-suppressive effect of stomatin on cancer cells (Figure 2B).

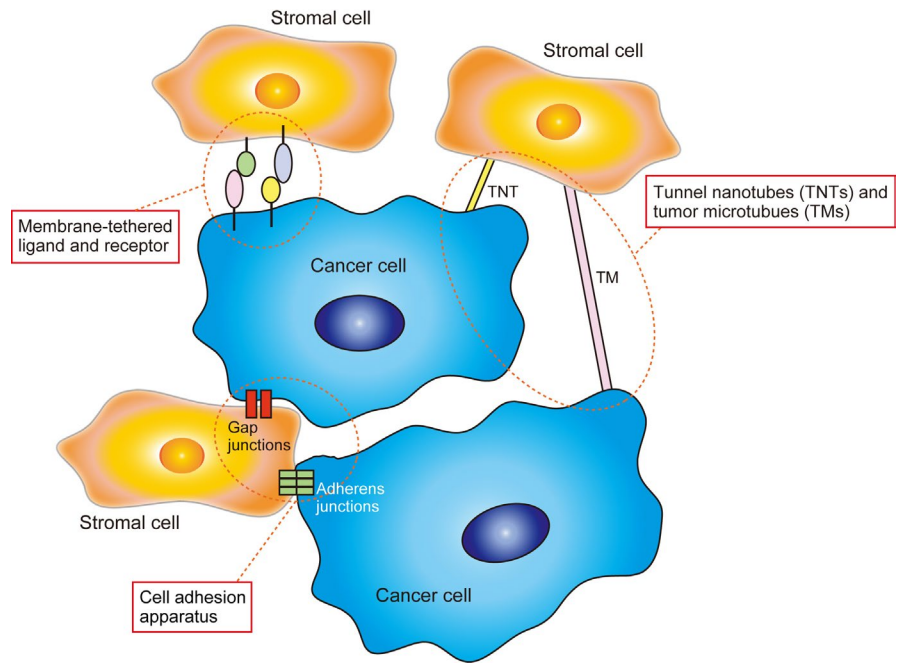
Consistent with our results, stomatin expression is decreased in malignant breast cancer positive for human epidermal growth factor receptor 2,³⁶ and stomatin inhibits tumor metastasis of non-small-cell lung cancer.³⁷ For other SPFH family members in cancer biology, stomatin-like protein 2 enhances the progression of several types of cancers,^{38,39} and its overexpression in cancer cells predicts the poor prognosis of patients with colorectal and ovarian cancers.^{40,41} Prohibitin possesses tumor-suppressive and promotive functions.⁴² These activities depend on the intracellular localization of prohibitin. In the nucleus of a prostate cancer cell, prohibitin recruits Rb to suppress the transcriptional activity of E2F to inhibit the cell cycle.⁴³ In contrast, localization of prohibitin on the plasma membrane activates c-Raf and promotes cell adhesion and migration.⁴⁴ Flotillin expression, which is increased in multiple types of cancer, promotes tumorigenesis.⁴⁵ Together, these findings show that each member of the SPFH family plays a different role in tumor progression in a cell type-dependent manner.

Although stomatin possesses tumor-suppressive activity through targeting the HSP90-PDPK1-Akt signaling axis (Figure 2B), further studies are required to identify the mechanism of upregulation of stomatin expression in cancer cells subsequent to their direct contact with surrounding stromal cells. It has been reported that hypoxia and dexamethasone treatment induce stomatin expression in lung adenocarcinoma cells, and that dexamethasone effectively induces stomatin expression in concert with IL-6 stimulation.^{31,32,46} The wide range of pharmacological effects of dexamethasone against numerous diseases, including inflammatory diseases and cancers,^{47,48} indicate that it may be useful for anti-cancer therapy through increasing the expression of stomatin. Therefore, identifying the mechanism that regulates stomatin expression may lead to the development of novel anti-cancer therapeutics via stomatin-mediated tumor-suppressive effects.

3 | DIRECT CELL-TO-CELL CONTACT-MEDIATED REGULATION OF TUMOR BEHAVIOR

Several types of cell-to-cell contacts and communications occur during the direct interaction between cancer cells and stromal cells. These events are mainly categorized into the types as follows: contact via the molecules of the cell adhesion apparatus, contact between membrane-tethered ligands and receptors, and contact mediated by tunneling nanotube (TNTs) and tumor microtubes (TMs) (Figure 3). These molecules exert tumor-suppressive or promotive functions, or both, in the tumor microenvironment.⁸

FIGURE 3 Intercellular communication between cancer cells and stromal cells mediated by the cell adhesion apparatus, membrane-tethered ligands and receptors, and tunneling nanotubes (TNTs) and tumor microtubules (TMs)



3.1 | Intercellular contact via the molecules of the cell adhesion apparatus

Adherens junctions and gap junctions, which participate in forming direct connections between neighboring cells including cancer cells and stromal cells, are essential for diverse cellular functions.^{8,49} Adherens junctions mainly consist of transmembrane cell adhesion molecules, such as cadherins and nectins, and scaffold proteins that bind to the intracellular region of cell adhesion molecules to stabilize their cell surface localization.⁵⁰ Invasive cancer cells usually contact stromal cells through cell adhesion molecules of adherens junctions.^{51,52}

Heterotypic interactions between N-cadherin in cancer-associated fibroblasts and E-cadherin in cancer cells generate intercellular physical forces to promote collective invasion of cancer cells.⁵² Expression of E-cadherin in cancer cells often switches to that of N-cadherin, particularly during the epithelial-mesenchymal transition.⁵³ This switch promotes cancer cell invasiveness and metastasis via N-cadherin-enhanced fibroblast growth factor signaling. Such signaling increases the expression and secretion of matrix metalloproteinase-9 and the physical contact between cancer cells and the endothelium and stroma.⁵⁴ Invasive cancer cells and stromal cells express other cadherins such as cadherin-11 and cadherin-23, which support the physical contact between cancer and stromal cells, contributing to tumor aggressiveness.^{55,56} Cancer cells that express VE-cadherin interact with endothelial cells to promote neovascularization.⁵⁷ Furthermore, such vasculogenicity mediated by the cooperation of tumor cells with endothelial cells in the tumor microenvironment occurs in several types of aggressive cancers.⁵⁸

Gap junctions comprise arrays of intercellular channels formed by connexin proteins. Connexins are integral membrane proteins that constitute a family of 21 members in humans. Connexin-mediated junctions permit the bidirectional transfer of ions, metabolites, and

secondary messengers between adjacent cells.⁵⁹ Evidence indicates that connexins function as tumor suppressors or promoters, depending on the isoform, tumor stage, and tissue.⁶⁰ Gap junctions formed between cancer cells and immune cells suppress tumor growth.^{61,62} Gap junctions between cancer cells and endothelial cells negatively regulate angiogenesis and positively regulate metastasis.^{63,64} The involvement of connexins in establishing intercellular communication between malignant tumors and astrocytes provides advantages for tumor invasiveness and resistance to chemotherapy via transfer of tumor-protective miRNAs and cyclic GMP-AMP (a second messenger that stimulates the production of interferon) from astrocytes to cancer cells.^{65,66}

3.2 | Intercellular contact between membrane-tethered ligands and their receptors

Direct contact of cancer cells with stromal cells in the tumor microenvironment is mediated by the interaction between a membrane-tethered ligand and its receptor. Eph receptor tyrosine kinases and their ligands ephrins bidirectionally signal to mediate tumor progression.⁶⁷ Early during the development of the tumor microenvironment, the tumor-suppressive effect of Eph-induced signaling is enhanced by ephrins expressed in surrounding normal cells, inhibiting the expansion and invasiveness of tumors that express Eph receptors.^{68,69} However, during the late stage, unconventional ephrin-independent Eph signaling activities promote cancer progression.⁷⁰ In addition, activation of EphA4 signaling in breast cancer cells is induced by tumor-associated macrophages expressing ephrins, facilitating cytokine release from cancer cells to sustain the cancer stem cell niche.⁷¹ Another signaling between membrane-tethered ligands and their receptors is Notch signaling between cancer cells and stromal cells that contributes to tumor

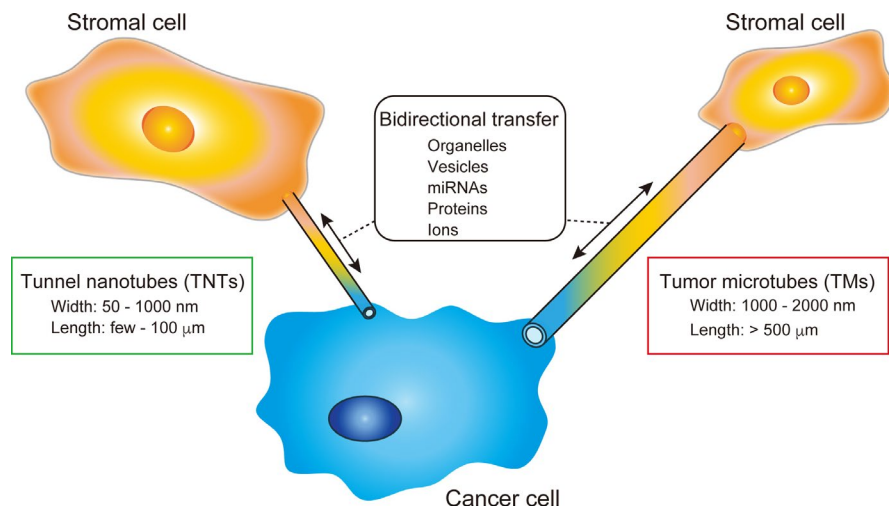


FIGURE 4 Structure and function of tunneling nanotubes (TNTs) and tumor microtubes (TMs)

progression at various stages.⁷² In colorectal cancer, activation of the Notch1 signal triggered by its ligand delta-like ligand 4 in endothelial cells stimulates endothelial transmigration, resulting in the promotion of metastasis.⁷³ Endothelial cells provide another Notch ligand, Jagged-1, to activate Notch1 on glioblastoma cells to nurture self-renewal of cancer stem-like cells.⁷⁴ Activation of the Notch3 signal in breast and ovarian cancer cells by Jagged-1 in their surrounding cells increases their chemotherapy resistance and proliferation.^{75,76}

It is well known that the interaction of the membrane-tethered ligand programmed cell death-ligand 1 (PD-L1) in cancer cells with its receptor PD-1 in effector T cells suppresses the T cell-mediated anti-tumor immune response and induces cancer progression.⁷⁷ Furthermore, this interaction may provide cancer cells with multidrug resistance by upregulation of P-glycoprotein expression through the phosphatidylinositol 3-kinase/Akt and mitogen-activated protein kinase pathways downstream of PD-L1.⁷⁸

3.3 | Molecules involved in intercellular communication mediated by TNTs and TMs

Recently, newly identified types of intercellular communication, designated TNTs and TMs, function in normal cells as well as in cancer cells (Figure 4). TNTs and TMs are F-actin-containing thin membranous channels that differ in size to enable direct communication between cancer cells and stromal cells over long distances. These tubular structures allow the rapid exchange of cellular components and molecules, including organelles, vesicles, molecules, and ions.⁷⁹ The formation of TNTs requires a complex comprising M-Sec and the GTPase RALA to regulate the generation of F-actin.⁸⁰ In macrophages, loss of function of M-Sec disrupts TNT-mediated communications with cancer cells, and suppresses invasive tumor morphology.⁸¹ Deficiency of connexin-43, which stabilizes the connection of TMs to cells, reduces the TM-mediated network between tumor cells and astrocytes, resulting in the suppression

of glioblastoma cell proliferation.⁸² However, TNTs and TMs are newly identified mediators for direct intercellular communications and, therefore, further investigations are required to establish their importance in the reciprocal interaction between cancer cells and stromal cells.

4 | CONCLUSIONS

Cell-to-cell contact-mediated communications between cancer cells and surrounding stromal cells direct tumor behavior through promotive or suppressive activities, which often depend on the stage of tumor development and the types of tumors and stromal cells. We have recently found that the genes encoding EMP1 and stomatin are upregulated in cancer cells specifically associated with stromal cells. Among the abovementioned three types of direct cell-to-cell contacts, cell adhesion might be important for induction of the expression of EMP1 and stomatin by the following studies. A member of epithelial cell adhesion molecule, trophoblast cell surface antigen 2, maintains the expression of EMP1 in cholangiocarcinoma cells.⁸³ In stomatin expression, it is upregulated by IL-6,⁴⁶ for which secretion is regulated by cell adhesion molecule cadherin-11 as well as inflammatory cytokines.⁸⁴

Furthermore, EMP1 and stomatin positively and negatively regulate cancer progression, respectively. Therefore, in addition to the actions of extracellularly secreted factors, direct cell-to-cell contact-mediated gene expression and direct intercellular communication spatiotemporally contribute to the determination of tumor characteristics. Identification of other molecules that mediate mutual intercellular communication between cancer and stromal cells may provide key insights into the regulation of cancer progression.

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DISCLOSURE

The authors declare no conflict of interest.

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