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Tumor Discovery

MINI-REVIEW

Exploring the cell-to-cell communication network to better defeat cancer

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Abstract

Just like us, cells communicate, but in their own unique way. Using waves as their common language, cells signal to each other about where and when to move. They talk, share information, and collaborate. The human body comprises trillions of cells that continuously adapt to their surroundings, exchanging millions of vital signals for survival. This communication must be meticulously regulated, as any disruption can lead to errors, such as the abnormal cell growth observed in cancer. The interaction between cancer cells and their neighboring cells is bidirectional, involving a complex network of mechanisms that can drive aggressive tumor behaviors—such as rapid growth, spread, and treatment resistance—or, conversely, act to suppress malignancy. This dynamic interplay within the tumor microenvironment unfolds through two primary modes: direct communication through physical cell contact, mediated by adhesion molecules, electrical signals, or the exchange of materials through gap junctions, and indirect communication facilitated by paracrine signaling. The latter involves the release of signaling molecules like cytokines, growth factors, and extracellular vesicles. Disrupting these cellular dialogues presents a promising therapeutic frontier. Specifically, strategies that integrate interventions targeting tumor communication pathways with conventional chemotherapy could enhance treatment efficacy, offering a synergistic approach to hinder cancer progression and improve outcomes. This article delves into the role of cell-to-cell communication in cancer development, its impact on metastasis, and how ongoing research is broadening our understanding of the disease.

Keywords: Cell; Communication; Cancer; Microenvironment; Metastasis

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1. Introduction

Cell-to-cell communication refers to the way cells interact to maintain homeostasis or normal functioning. It is similar to a conversation between people, where one cell sends signals or engages in physical interactions, and the receiving cell responds accordingly. For instance, a cell might express and/or secrete a peptide or a ligand, which a neighboring cell receives, interprets, and acts upon. This process is crucial for normal human tissue development and functioning, particularly in the differentiation and specialization of cells, such as stem cells.[1]

Cells communicate in various ways, such as secreting hormones that bind to receptors on neighboring cells and through direct surface contact. These signals and interactions regulate cell growth, death, and differentiation.[2] In cancer, this communication is

disrupted by cells sending out erroneous signals, creating a self-serving microenvironment that evades normal cell-to-cell cues.[3] For example, if one cell has a mutation and no longer responds to signals from another adjacent cell, it can grow uncontrollably and form a tumor. Cell-to-cell communication plays a crucial role in tumor development and clonal evolution by enabling cancer cells to reprogram the surrounding tumor microenvironment (TME) and immune cells.[4] This communication supports processes essential for tumor development and spread, such as angiogenesis, immunoediting or immunosuppression, invasion, and multi-drug resistance.

Cell-to-cell communication can occur through membrane receptors and ligands or via soluble molecules like growth factors, cytokines, and chemokines. In addition, microRNAs and extracellular vesicles have recently been identified as additional means of cell communication.[5] Circulating nucleic acids are often deregulated in many cancers and, as they affect all the disease's hallmarks, they may serve as valuable biomarkers for cancers. Meanwhile, extracellular vesicles released from cancerous cells contribute to tumor growth and distribution.

2. The community of cancer cells with their own language

Two broad themes have emerged in recent years that have changed our perspective on cancer. First, cancer cells are not only communicating with their environment and each other but also with normal cells in the body, such as cancer-associated fibroblasts or neurons. Second, cancer cells are not merely growing uncontrollably and ignoring their surroundings; instead, they are strategically coordinating actions among themselves as a community.

Unlike the relatively slow, soluble signals produced by ligands released from a cell towards a receptor over a short distance, electrical pulses might offer a rapid and distant transmission system, similar to quorum sensing in bacteria and electrical signals used by fungi. It is conceivable that similar quorum sensing systems exist in communities of cancer cells, allowing them to communicate about nutrient locations and coordinate their metabolism. Once predictable classes of communication signals are identified, we can start to see the building blocks of a code or language, where different patterns might be interpreted differently by various cells (Figure 1). Disrupting these signals could dysregulate the community, much like an army without its general. The challenge lies in understanding the language but not yet knowing the cellular response.

As tumors progress, cancer cells acquire hallmark capabilities that enable unchecked malignancy. These include autonomous growth (not triggered by external growth signals), tissue invasion and metastasis, angiogenesis induction, and evasion of proliferative restraints like apoptosis and senescence. These traits stem from dysregulated signaling pathways that normally regulate cell division, survival, and motility in healthy tissues. Many experimental cancer therapies now focus on targeting these aberrant signaling molecules — key drivers of oncogenic behavior.

Emerging research highlights that specialized cell-cell adhesion complexes, critical for maintaining epithelial polarity and tissue structure, undergo dramatic remodeling during epithelial-to-mesenchymal transition (EMT).[6] As EMT begins, these structures undergo disassembly, dismantling cell-cell adhesion while redistributing or degrading junctional proteins. Among these, adherens junctions act as central regulators, coordinating the integrity of the entire junctional network—including tight junctions and desmosomes. Cadherins, the transmembrane proteins within adherens junctions, directly mediate intercellular adhesion.[7] Notably, E-cadherin—a hallmark of healthy epithelial tissues—is frequently lost in metastatic cancers, and experimental suppression of its function transforms epithelial cells into invasive, motile populations.[8] This shift often coincides with upregulated N-cadherin expression, a process termed cadherin switching, which is tightly linked to tumor progression.[7]

The TME is a pathologically altered ecosystem that dynamically evolves during cancer progression, driven by intricate cell-cell signaling networks.[9] Integrating multi-omics data offers a powerful lens to map tumor heterogeneity and decode the complex signaling pathways underlying these interactions.[10] Deciphering the unique molecular pathways driving tumor subtypes enables the discovery of novel therapeutic targets, paving the way for precision therapies tailored to each subtype's molecular profile.[11]

3. Drug-resistant tumor cells communicate directly with immune cells

Cancer cells are not only influencing healthy surrounding tissues with their communication tactics. There is growing evidence that tumors can signal directly to non-cancer cells within the TME. As cancer cells evolve, they acquire resistance to therapy by altering communication with non-malignant cells in the TME (Figure 2). However, the specific interactions between malignant and non-malignant cells that cause this drug resistance remain largely unknown.

Scientists have employed advanced single-cell RNA sequencing to determine the gene expression profile and an immune cell classifier to understand the immune composition of the different tumor biopsy samples.[12]

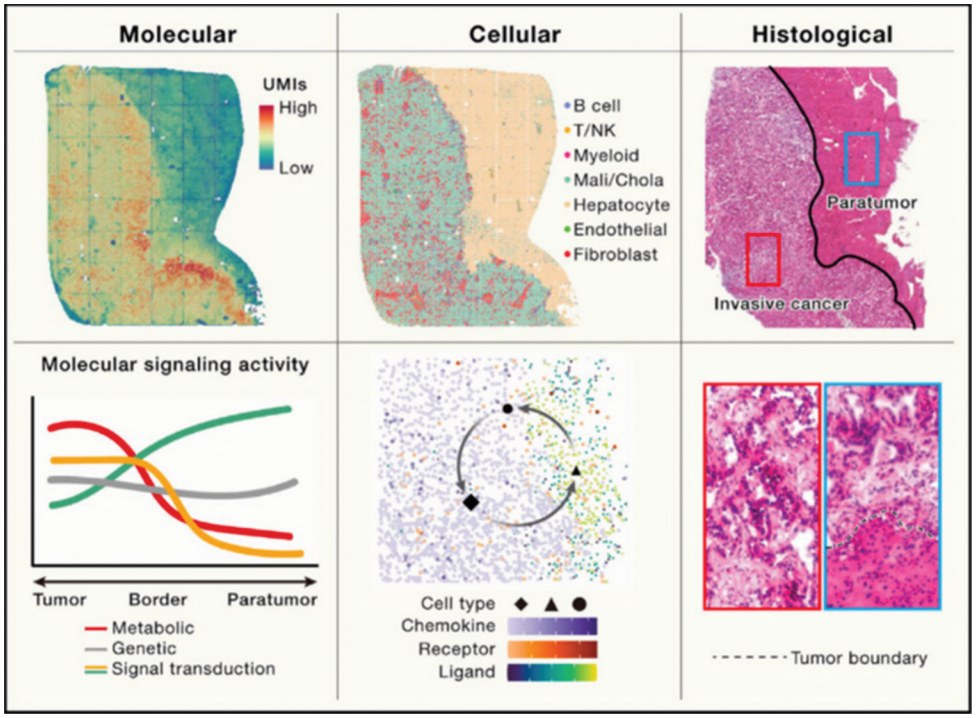


Figure 1. Illustration of how decoding of cell-to-cell communication and signaling can uncover pathogenesis and therapeutic strategies of cancer. The figure was created with BioRender.com.

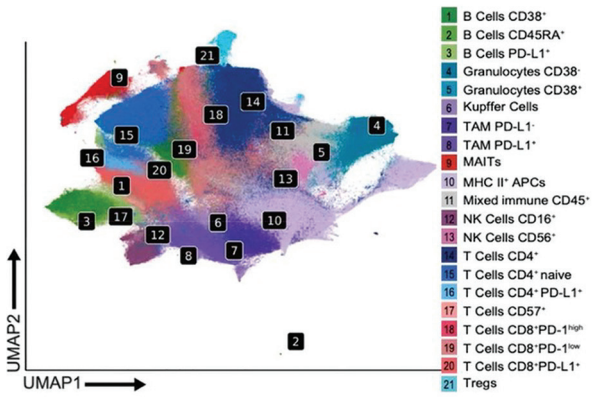


Figure 2. A representative tumor tissue image showing immune cell-type annotation in tumor microenvironment which is segmented to identify individual cells and their associated marker expression profiles. Figure was created using ×10 Genomics Visium Spatial Software Suite.

Their study produced an overall network map of how strongly these cell types are communicating. The results of this network analysis is that the resistant tumor cells lacked normal communication with immune cells but were sending plentiful immunosuppressive signals to macrophages. Cancer cells can alter the phenotypes of macrophages and myeloid cells, and the role of cancer-associated fibroblasts and endothelial cells that can support the growth of the cancer by producing capillary network that provides resources have been described previously.[13] What was unclear before this study was which of these cell types play these roles.

Preclinical research highlights that immune evasion mechanisms emerge early in tumor development. For example, single-cell analysis of premalignant mammary tumors (driven by *BRCA1* and *p53* mutations in a transgenic model) uncovered immunosuppressive microenvironments marked by elevated regulatory T cells (Tregs) and tissue-resident macrophages, even at precancerous stages.[14] Parallel findings in pancreatic cancer models revealed that mutant KRAS-driven lesions progress faster when combined with tissue damage mediated by the pro-inflammatory signal interleukin (IL)-33.[15] Administering IL-33 to mice with KRAS mutations induced epigenetic dysregulation and accelerated pancreatic intraepithelial neoplasia, demonstrating how environmental stressors interact with genetic changes to activate cancer-promoting pathways. These studies underscore that the timing and drivers of immune evasion during tumor initiation vary depending on tissue type, initiating mutations, and host factors.

Chronic inflammation creates a permissive environment for cancer development by hijacking immune cell interactions that suppress anti-tumor defenses. Inflamed tissues often exhibit Th2-polarized immunity

and an influx of immunosuppressive myeloid cells, which release reactive oxygen species, pro-inflammatory cytokines, chemokines, and angiogenic factors. These mediators drive tissue damage, DNA mutations, vascular dysfunction, and matrix remodeling—processes that fuel tumor initiation and progression.[16] Classic examples include inflammatory bowel disease (linked to colorectal cancer), chronic hepatitis or fatty liver disease (associated with hepatocellular carcinoma), and asbestos-induced inflammation (a precursor to mesothelioma). Obesity-related inflammation similarly elevates risk for malignancies such as breast and endometrial cancers.[17]

Whether tumors arise from pre-existing inflammation or trigger inflammation during early growth, most cancers share mechanisms to evade immune surveillance. Progressing tumors frequently exclude or impair anti-tumor immune cells (T cells, natural killer cells, and dendritic cells) while recruiting pro-tumor myeloid populations like macrophages and neutrophils.[18,19] This dual strategy fosters an immunosuppressive, pro-angiogenic niche that supports tumor survival and spread.

4. Long-range cell communication via tumor exosomes

Exosomes are extracellular vesicles ranging from 30 to 150 nm in diameter, released by various cell types, including tumor cells. They can induce apoptosis, modulate the immune system, and serve as biomarkers for diagnosis. As a crucial component of cell-to-cell communication, exosomes regulate the TME and are involved in the development, progression, and metastasis of numerous cancers.[20,21]

Tumor-derived exosomes contain proteins, nucleic acids, lipids, and metabolites that act as effective messengers between tumor cells and various other cells, including immune cells, vascular endothelial cells, and mesenchymal cells (Figure 3). This communication significantly impacts tumor biological activities such as immune regulation, angiogenesis, and EMT, which in turn influence tumor cell growth, proliferation, and metastasis.[22]

Emerging research underscores exosomes as dynamic mediators of intercellular communication, facilitating the transfer of proteins, mRNAs, miRNAs, and oncoproteins to recipient cells.[23] These cargo molecules modulate diverse processes such as immunoregulation, extracellular matrix remodeling, and growth factor signaling, which collectively influence tumor progression.[24] Within the TME—a network of tumor-associated fibroblasts, immune cells, and osteoblasts—exosomes play multiple roles: they enhance tumor cell proliferation, confer chemotherapy resistance, and regulate stromal cell behavior. Stromal cells in the TME internalize exosomal miRNAs, mRNAs, and proteins, which subsequently orchestrate pro-tumorigenic signaling cascades.[25]

Targeting tumor-derived exosomes may positively impact cancer therapy. Exosomes secreted by malignant cells have a tumor-promoting effect, and tumor cells generally secrete more exosomes than normal cells. These secretomes carry mRNA, miRNAs, lncRNAs, and proteins that can serve as biomarkers for cancer diagnosis and prognostic monitoring.[26] In addition, exosomes play a crucial role in therapy resistance. They carry specific payloads that can transfer resistant phenotypes to sensitive cancer cells, conferring resistance to chemotherapy and radiation by altering the cell cycle and inducing anti-apoptotic processes. Exosomes may also inhibit the entry of chemotherapeutic agents into target cancer cells, affecting the efficacy of chemotherapy.[21] Therefore, targeting tumor exosomes may offer a new direction for cancer therapy, and relevant clinical trials are already underway.

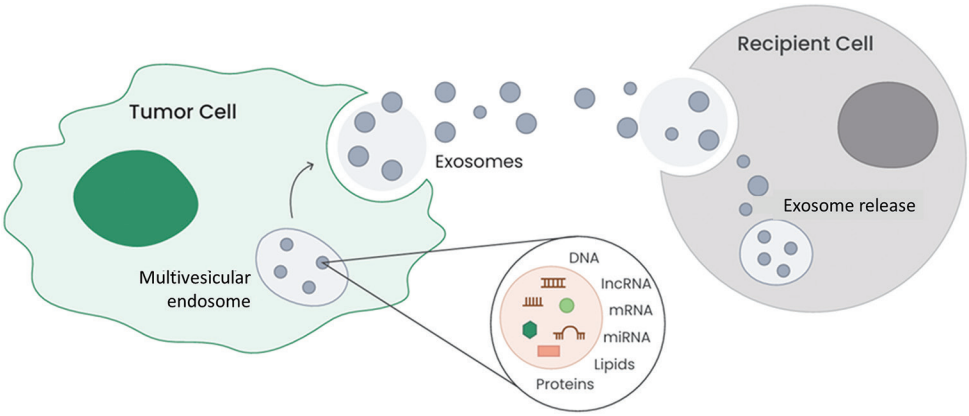


Figure 3. Exosomes mediate cell–cell communication locally and systemically. When reaching the recipient cell, tumor-derived donor exosomes can either trigger signaling by directly interacting with extracellular receptors or be uptaken by direct fusion with the plasma membrane and get internalized. The figure was created with BioRender.com.

4.1. Cell-to-cell communication and metastasis

Metastasis occurs when cancer cells detach from their original site and travel through the bloodstream to establish themselves in other organs, such as the lungs, bones, brain, or liver. Metastasis is the leading cause of death from cancer.[27] The primary tumor rarely causes death; instead, it is the formation of new tumors in distant organs that leads to patient mortality. The process of metastasis is highly inefficient, requiring cancerous cells to undergo numerous changes to survive their journey and thrive in a new environment. Intercellular communication enhances this process in various ways. For instance, tumor cells may collaborate with lymphocytes and/or macrophages to create a pro-tumor environment.[28] Tumor cells sometimes migrate together, resembling an island moving through the bloodstream with its own microenvironment, in search of a new site. These cells alter their communication with non-cancerous cells, such as those in the vasculature or immune system, to ensure their survival. This cell editing process generates signals that favor and support the tumor cells rather than normal cells.[29]

Migrating tumor cells, known as circulating tumor cells (CTCs), have been found to have a significantly higher success rate in forming metastatic tumors when they cluster together—up to 50 times higher.[30] Cell-to-cell communication within the CTC cluster helps these tumor cells survive the harsh environments they encounter during metastasis. In the bloodstream, CTCs face strong physical pressures from flow and constriction, as well as attacks from immune cells. In distant tissues, the growth environment differs greatly from the original tissues, causing many CTCs to die or cease growing permanently. However, CTCs in a cluster gain protection through cell-to-cell communication, enabling them to survive in the bloodstream and successfully regrow in distant organs.[31] Investigators have thereby focused on rapidly testing patient tumor cells for metastatic potential rather than growth. This approach allows scientists to determine within a few hours which drugs can most effectively reduce the risk of metastasis for the specific cells from a patient's tumor.[32]

The electrical activity of cells has been associated with cancer's ability to metastasize. Research has shown that prostate cancer cells can modify their baseline voltage to open sodium ion channels in their membranes. By opening these channels, cancer cells allow ions to enter, increasing their likelihood of metastasizing. Conversely, closing these channels could potentially prevent metastasis.[33] On the other hand, the loss of function of the sodium leak channel non-selective protein (NALCN) in gastrointestinal cancers promotes metastatic disease by increasing the release of CTCs. By considering metastasis as a "normal phenomenon" rather than something unique to cancer, the researchers found that NALCN regulates the dissemination of both normal and cancerous epithelial cells, thereby distinguishing the process of metastasis from cancer.[34] These normal disseminated epithelial-like cells can "metastasize" to distant organs. However, instead of forming tumors, they integrate into normal structures within these tissues, such as kidney tubules. For this process to occur, the seeded circulating epithelial-like stem cells must interact with neighboring cells in their new environment to mimic or adapt to a new cell state.

5. Cell communication research is changing the face of cancer treatment

Research has transformed our understanding of cancer and, consequently, our approach to treatment. We now know that different parts of a tumor communicate to coordinate growth, and blocking this communication could lead to new treatment strategies. Additionally, tumor cells can disguise themselves, tricking the immune system into perceiving them as "normal" cells. They engage with receptors to mask the tumor, adopting the tissue's features to blend in. This cell-to-cell communication allows tumor cells to interact with normal cells, enabling their survival. Significant efforts and technological advancement are underway to disrupt this masking process and reveal the true identity of tumor cells (Figure 4). For instance, immune checkpoint inhibitors are being used to block the masking signals, allowing the immune system to recognize and inhibit tumor cells.[35]

Several types of immunotherapies are effective in treating cancer, including monoclonal antibody therapies designed to recognize specific proteins on cancer cells, mimicking the body's natural response. These therapies hijack cell-to-cell communication, allowing drug treatments to be delivered directly into the tumor to kill the disease. Examples include trastuzumab and rituximab, which work in different ways to either kill cancer cells or stop them from growing.[36] Another approach is chimeric antigen receptor T-cell therapy, a type of adoptive cell transfer. This involves harvesting a patient's immune cells and modifying them to recognize and target tumor cells. A receptor designed to identify a specific protein on the cancer cells is added to the immune cells. Once these modified cells are administered back to the patient, they target and kill the tumor.[37]

Future treatments will continue to focus on blocking cell-to-cell communication, and several existing therapies are already used to treat breast cancer. These include selective estrogen receptor modulators like tamoxifen and

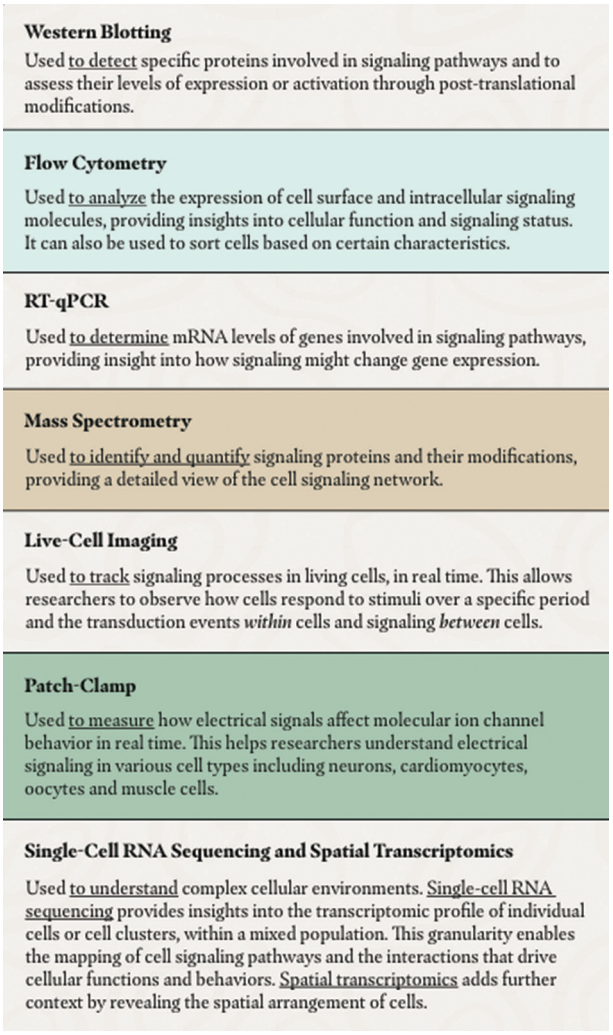


Figure 4. A list of advanced technologies used to analyze cell-to-cell communication and signal transduction in the complex tumor microenvironment. Researchers usually combine multiple technologies to minimize limitations and improve accuracy.

raloxifene, which block the estrogen signals that promote breast cancer cell growth.[38] Additionally, aromatase inhibitors such as letrozole, anastrozole, and exemestane work by blocking estrogen production.[39] Research is increasingly focusing on metastasis due to the scarcity of drugs targeting these metastatic steps and the limited options for closely monitoring the metastasis process in patients.

6. Conclusion

For many years, tumors were seen as masses of rogue cells growing uncontrollably due to abnormal cell signaling pathways. However, as our understanding of the disease deepens, it becomes clear that the communication pathways cancer cells use among themselves and with their microenvironment are far more sophisticated.

Cancer cells engage in complex interactions with neighboring cancerous and stromal cells through direct cell-to-cell contact and paracrine signaling. Long-range communication with distant organ sites is facilitated by extracellular vesicles, exosomes and signaling molecules such as cytokines, hormones, and growth factors. These signaling events are crucial for cancer cell survival, metastasis, and immune evasion. To effectively combat cancer initiation, progression, and metastasis, it is essential to understand how cancer cells communicate within their microenvironment and with distant organ sites.

As cancer evolves and evades treatment, therapies must also adapt. New research, particularly on cell-to-cell communication, is continually enhancing our understanding of how to treat and manage this devastating disease.

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Conflict of interest

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Author contributions

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Writing – original draft: Chen Yeh
Writing – review & editing: All authors

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Consent for publication

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Availability of data

Not applicable.

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