# CELL FUSION: A PROMISING TARGET FOR CANCER IMMUNOTHERAPY

**Abstract**

Cell-cell fusion is a fundamental biological process with vital roles in various physiological functions, including fertilization, placental development, muscle formation, and tissue regeneration. However, this process also has implications in cancer biology, as both normal and cancer cells can exploit it to promote malignancy and contribute to tumor evolution. When cancer cells fuse with immune cells, known as fusion hybrids, they acquire properties that enhance tumoral proliferation and leucocyte mobility, facilitating metastatic spread. Additionally, cell fusion leads to genetic and transcriptomic reshuffling, resulting in the development of drug resistance in cancer cells. Understanding the intricate mechanisms of cell fusion is crucial for devising targeted therapies aimed at disrupting, thus impeding tumor growth and metastasis. Within this chapter, we delve into the critical role that cell fusion plays in cancer biology and its potential implications for cancer treatment, especially in the realm of immunotherapy. By comprehending the intricate processes of cell fusion, researchers can glean invaluable insights into how cancer cells interact with their microenvironment and evade immune surveillance. These discoveries present exciting prospects for pioneering novel approaches to combat cancer and other diseases effectively.

**Keywords:** Fusion Hybrids, Metastasis, Drug resistance, immune evasion, immune surveillance

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## I. INTRODUCTION

Cell-cell fusion is a key physiological process that underlying the merging of two or more cells to generate hybrid cells [1]. This complex process contributes to tissue homeostasis and regeneration in organs like the liver, brain, muscle, and lung and is essential for many physiological processes, such as fecundation, placentation, muscle growth, and osteoclast differentiation [2]. Cell-cell fusion has an impact on cancer biology in addition to its physiological importance. It can be used by both healthy and malignant cells to promote malignancies and aid in the development of tumours[3], [4]. The genetic and phenotypic characteristics of each parental cell are united during fusion, resulting in hybrid cells that inherit the characteristics of their parents[5].

This behaviour has been widely documented, especially when cancer cells combine with immune cells like leucocytes to form hybrid cells that can both proliferate tumours and mobilise leucocytes, which aids in the spread of metastatic disease[6], [7]. Cell-cell fusion also introduces genetic and transcriptome reorganization, which bestows novel traits on the hybrid cell[8]. Recent research has shown that cell fusion plays a crucial role in the growth and development of tumors since it not only contributes to tumour initiation and relapse but also confers medication resistance [9]. As the only technique facilitating horizontal genetic transmission by fusing different genomes, cell fusion distinguishes itself from other mechanisms of genome remodelling, such as chromothripsis or cytokinesis oversights.

According to Hernandez and Podbilewicz ([10]), the cell fusion process entails a dynamic series of actions that can be broken down into three major phases: cell preparation, membrane interaction via the effect of fusogens, and lipidic rearrangements to generate the new cells. The initial step of cell-cell fusion involves preparation for the fusion event. Cells receive and respond to extracellular signals, which may induce cell differentiation and activation of specific signaling pathways. This process sets the stage for subsequent interactions between the fusing cells.Cell fusion typically begins with the recognition and adhesion of two neighbouring cells. This step involves interactions between specific molecules on the cell surfaces, enabling the cells to adhere to each other. As the fusing cells recognize and interact with each other, they adhere tightly, and the distance between them decreases to less than 10 nanometers. Fusogens (Box 1), specialized proteins, start to take over at this point. The final approach between the fusing cells' membranes is mediated by these fusogens. The fusogens help to create fusion pores and start the merging of membranes. Fusogens govern a number of morphological changes that occur during the fusing of cell membranes. Dehydration, hemifusion (including unilateral and bilateral fusion), and pore opening and expansion are some modifications. Dehydration is the first stage of membrane union, which removes water from the space between the contacting membranes. Hemi fusion is the term used to describe the partial fusion of the cell membranes' outer leaflets. The development and enlargement of fusion pores, which allow the interchange of cellular contents between the fusing cells, are involved in pore opening and expansion[11], [12].The final step of the cell fusion process results in the constitution of a new single hybrid cell. This hybrid cell shares all cytoplasm and genetic material from both parent cells, resulting in a unique cellular entity with a combined genetic makeup and cellular components.

Cell fusion is a complex biological process that involves various signaling pathways to regulate and coordinate the fusion of two or more cells. Fusogens, such as Syncytin-1 and Syncytin-2, play a crucial role in the initial recognition and interaction between fusing cells,

 

leading to the formation of fusion pores and eventual membrane merging. The expression of Syncytin-1 is tightly regulated through specific transcription factors like GCM1, along with epigenetic modifications like DNA methylation and his tone acetylation[13], [14]. Notably, the Wnt/β-catenin signaling pathway has been shown to target the GCM1/syncytin pathway, upregulating Syncytin-1 expression and promoting cell fusion events[15]–[17]. Rho family GTPases, including RhoA, Cdc42, and Rac1, regulate the necessary cytoskeletal rearrangements for cell fusion, influencing actin dynamics essential for membrane protrusions and cell-cell contact. Calcium signaling, with increased intracellular calcium levels, triggers fusion pore opening and content mixing between fusing cells. Specialized calcium-dependent fusion proteins, such as synaptotagmins and syncytins, facilitate membrane fusion. Furthermore, the Wnt, Notch, and JAK-STAT signaling pathways have also been implicated in regulating cell fusion events in various developmental contexts[18], [19]. The specificity of signaling pathways involved in cell fusion can vary depending on cell types and biological context, and ongoing research aims to fully elucidate the intricate regulatory mechanisms governing this process.

This book chapter explores the significance of cell fusion in cancer biology and its implications for cancer treatment, particularly in the context of immunotherapy. By understanding the complex mechanisms of cell fusion, researchers can gain valuable insights into how cancer cells interact with the surrounding microenvironment and evade the immune system. This knowledge opens up new possibilities for developing targeted therapies that disrupt or prevent cell fusion events, impeding tumor growth and metastasis effectively. Furthermore, fusion hybrids resulting from cell fusion could serve as specific targets for novel anti-cancer drugs, paving the way for advancements in cancer treatment. The study of cell fusion and its role in cancer immunotherapy holds immense promise for the future of cancer research, offering opportunities to improve existing therapies and explore innovative approaches to tackle cancer and other diseases.

## II. ROLE OF CELL FUSION IN CARCINOGENESIS

1. **Initiation:** Tumor Heterogeneity: Tumors are complex ecosystems consisting of genetically diverse cell populations with distinct characteristics. Tumor heterogeneity can arise through genetic mutations, epigenetic changes, and the selective pressures within the tumor microenvironment [20]. Cell fusion events introduce additional genetic diversity by bringing together cells with different genetic backgrounds, leading to the formation of tumor cell hybrids ([3]. Cell fusion can occur between tumor cells or between tumor cells and non-malignant cells, such as immune cells or stoma cells[21]. This fusion results in the combination of genetic material from the parent cells, leading to the generation of hybrid cells with diverse genomic profiles. The heterogeneous nature of tumor cell hybrids allows them to acquire a wide range of phenotypic traits, including increased proliferation, resistance to therapies, and enhanced invasive capabilities. This diversity creates a pool of cells with varied responses to treatment, making the tumor more challenging to manage.

    - **Polyploidy:** It refers to an abnormal state in which cells have multiple sets of chromosomes [22]. This condition can result from cell fusion events, leading to aneuploidy (abnormal chromosome number) in the resulting hybrid cells. When cells from different genetic backgrounds fuse, the chromosomes from each cell can

 

combine, leading to the formation of polyploid hybrid cells. These cells contain more than the typical diploid number of chromosomes. Polyploidy is associated with genomic instability and is a driving force in cancer development. Polyploid cells can undergo further genetic changes and contribute to tumor heterogeneity, as well as promote tumorigenesis by disrupting normal cellular processes and promoting aberrant cell division [23].

- **Cancer Stem Cells:** Cell fusion plays a pivotal role in generating cancer stem cells (CSCs), a unique and rare population within tumors that have significant implications in cancer biology. CSCs are responsible for initiating tumor growth and contributing to tumor heterogeneity, making them a critical target for cancer research and treatment strategies. The origin of CSCs is a subject of intense investigation, with two potential mechanisms being proposed[24], [25]. Firstly, it is postulated that adult stem cells, which normally have a self-renewal capacity and can differentiate into various cell types, may accumulate genetic aberrations over time. These accumulated genetic changes may lead to the transformation of these stem cells into CSCs with tumorigenic properties. Secondly, another mechanism involves cell fusion events between stem cells and differentiated cells. This fusion process can give rise to new cells with characteristics of both parental cells, leading to the formation of CSCs with stem-like properties and potential tumorigenicity. CSCs possess distinctive features that set them apart from other tumor cells [26]. One of the most significant aspects of CSCs is their resistance to conventional chemotherapy. This resistance is attributed to various factors, including their slow proliferation rate, enhanced DNA repair mechanisms, high expression of anti-apoptotic proteins, and over expression of ATP-binding cassette (ABC) multidrug pumps [27]. These features collectively enable CSCs to survive and persist in the face of cytotoxic treatments, leading to cancer relapse and treatment failure [28]. Moreover, CSCs are believed to have deregulated signaling pathways that control self-renewal in normal somatic cells. For instance, pathways such as Notch-signaling and Wnt/β-catenin signaling, which regulate self-renewal in normal stem cells, may be dysregulated in CSCs, leading to uncontrolled self-renewal and tumor growth [29]. Beyond their role in cancer relapse, CSCs are also implicated in tumor metastasis. It is hypothesized that CSCs possess the capacity to initiate and support the formation of distant metastases. Subpopulations of CSCs, such as primary CSCs (pCSCs) responsible for primary tumor formation and metastatic CSCs (mCSCs) driving metastasis, have been proposed based on their distinct roles in tumor progression [30]. Additionally, polyploid giant cancer cells (PGCCs) have emerged as an intriguing avenue for generating CSCs. These large cancer cells contain multiple copies of DNA and exhibit stem cell-like properties. They may arise through cell fusion events, contributing to tumor heterogeneity and chemo-resistance [31], [32]. Understanding the mechanisms of CSC generation is of utmost importance in cancer research and therapy development. Targeting CSCs directly may offer a promising approach to eliminate tumor-initiating cells and improve treatment outcomes for cancer patients. Identifying the factors that drive CSC formation through cell fusion and other mechanisms could lead to novel therapeutic strategies that disrupt CSC activity and ultimately lead to more effective and targeted cancer treatments.

 

Furthermore, research has shown that the fusion of tumour cells with somatic cells, stem cells, and bone marrow-derived cells may all aid in the development of CSCs. According to Gauck et al., spontaneous interactions between human breast cancer cells and breast epithelial cells produced hybrid cells that had CSC traits and improved colony formation capacity[33]. Similar to this, Zhang et al. found that heterotypic hybrid cells made of lung cancer cells and mesenchymal stem cells displayed stem cell markers at levels noticeably greater than their parent lung cancer cells[34]. Progenitor cells may acquire CSC and epithelial-mesenchymal transition (EMT) traits as a result of cell fusion, increasing their capacity for invasion and metastasis. These results suggest that the formation and maintenance of CSC populations within tumours may be significantly influenced by cell fusion events. Additionally, it has been found that the lymph node metastasis of breast cancer results in cell fusion between several cell types, with increased expression of the stromal marker vimentin and the breast stem cell markers CD44+/CD24- and decreased expression of the epithelial marker E-cadherin[35]. The progenitor tumour cells created by cell fusion may go through EMT and develop CSC traits, increasing their capacity for invasion and metastasis. Similar results were obtained when gastric cancer cells fused with mesenchymal stem cells, producing progenitor cells that expressed both mesenchymal and tumour stem cell markers more prominently. This finding suggests that cell fusion may result in the acquisition of a variety of stem cell-like characteristics [36].Furthermore, melanoma that had metastasized to a recipient of a bone marrow transplant was found to have malignant mononuclear cells, according to an article by LaBerge and colleagues. These cells had DNA from both the recipient and the bone marrow transplant donor, raising the prospect of in vivo spontaneous cell fusion between recipient and donor. These results highlight the possible importance of cell fusion events in the development of CSCs and in the heterogeneity and metastasis of tumours[37]. In conclusion, cell fusion is an important process for producing CSCs, which are crucial for the development, growth, and metastasis of tumours. Targeted medicines aimed at preventing CSC activity and enhancing the effectiveness of cancer treatment may find new applications if the molecular mechanisms behind cell fusion and CSC creation are better understood.

2. **Promotion:** Epithelial-Mesenchymal Transition (EMT): EMT is a complicated biological process in which epithelial cells adopt a mesenchymal phenotype with improved migratory and invasive abilities while losing their distinctive cell-cell adhesion qualities and polarised organization. EMT is essential for embryonic development and tissue regeneration, but it can be negatively impacted by cancer when it is dysregulated. Recent research has demonstrated that the EMT properties of the merged cells are stronger than those of the original cells when tumour cells fuse with somatic or mesenchymal stem cells. Human gastric cancer cells (HGC-27 and SJC-7901), human hepatoma cells (HepG2), human breast cancer cells (A549, H460, etc.), human lung cancer cells (A549, H460, etc.), and human endometrial cancer cells fusing with stromal cells are just a few examples of the many cases of tumour cell and normal cell fusion that have been documented in the literature. After cell fusion, hybrid progenies were created that exhibited EMT and were more capable of invasion, metastasis, and tumorigenesis than the parental cells (Xue et al., 2015; Dörnen et al., 2020b). Hematopoietic stem cells were shown to be able to fuse with normal human gastric mucosa cells (GES-1), which led to the discovery that the resulting cells not only experienced EMT but also displayed

 

malignant transformation of normal gastric mucosa epithelial cells (He et al., 2015). As revealed by Mortensen et al. (2004), human breast cancer cells have been shown to be able to fuse with endothelial cells, allowing the tumour cells to get through the endothelium barrier and facilitating metastasis.

**Clonal Expansion:** Clonal expansion refers to the proliferation and selective growth advantage of specific cancer cell populations within the tumor mass. This phenomenon is driven by genetic and epigenetic changes that confer growth advantages to certain cell clones. Following cell fusion, the resulting hybrid cells carry a combination of genetic material from both parent cells. If the hybrid cells acquire mutations or genetic alterations that promote rapid proliferation and survival, they gain a growth advantage over neighboring cells, leading to clonal expansion. Clonal expansion leads to the dominance of certain cancer cell populations within the tumor mass, contributing to tumor heterogeneity. Sub clones with aggressive characteristics can drive tumor growth, invade neighboring tissues, and metastasize, further enhancing tumor progression and malignancy.

3. **Progression:** Cancer Angiogenesis: Tumor progression, invasion, and metastasis depend critically on tumor angiogenesis, a process by which tumors induce the formation of new blood vessels to sustain their growth. Despite considerable research efforts, the precise mechanisms governing tumor angiogenesis remain enigmatic. According to current research, tumor cells obtain vascular supply by a variety of mechanisms, including vascular mimicry (VM), mosaic blood vessels, and endothelial cell-dependent blood vessels. The critical function of tumor cell fusion events with host cells such white blood cells, macrophages, cancer stem cells (CSCs), and mesenchymal stem cells in promoting tumor invasion and metastasis is particularly highlighted by new research. The progenitor tumor cells that develop from the fusion of tumour cells with bone marrow-derived cells have properties similar to those of the bone marrow-derived cells. Increased angiogenesis and cellular activity result from this change, which may play a significant role in the growth and metastasis of tumours. Investigations have also shown that glioma stem cells and bone marrow mesenchymal stem cells both significantly contribute to tumour angiogenesis through cell fusion, demonstrating the variety of functions that cell fusion plays in this complex process (Sun et al., 2019).

The emergence of cancer stem cell-like cells, known as polyploid giant cancer cells (PGCCs), through cell fusion adds yet another dimension to the saga of tumor angiogenesis. PGCCs possess unique properties that facilitate tumor angiogenesis through trans differentiation and participation in VM formation. PGCCs coordinate VM structures when combined with their erythroid progeny, offering a different route for tumour growth, invasion, and metastasis. VM structures effectively maintain an ongoing flow of blood and oxygen to enable tumour growth by interacting with endothelial cell-dependent channels (Zhang et al., 2014c; Yang et al., 2018). Remarkably, recent discoveries have illuminated the ability of PGCCs to generate red blood cells bearing characteristics of embryonic and fetal haemoglobin. This characteristic gives tumour cells a strong affinity for oxygen, giving them an advantage in environments with severe hypoxia and supplying them with an abundance of energy and oxygen to promote tumour invasion and metastasis (Zhang et al., 2015; Li et al., 2021). Tumour cells can initiate PGCC creation through cell fusion in response to a variety of stimuli, resulting in CSC-like traits, hematopoietic cell differentiation, and VM development (Hassan and Seno, 2020).

 

The intricate interplay between cell fusion, tumor angiogenesis, and PGCCs continues to captivate researchers, unraveling new avenues for understanding the relentless progression of cancer. As scientific investigations delve deeper into the realm of cell fusion and its implications in angiogenesis, we advance toward unveiling the elusive secrets that underpin tumor growth, with implications for innovative strategies to counteract cancer's relentless advance.

## III. IMPLICATIONS OF CELL FUSION

1. **Metastasis:** The most lethal feature of cancer, known as metastasis, is the spread of cancer cells from the initial site to distant organs and tissues, which causes the development of secondary tumors [38]. In addition to their fundamental properties, cancer cells are affected by interactions with the stroma around them, which is made up of benign and malignant cells in nearby and remote microenvironments. The relationship between the tumour and the stroma, which consists of fibroblasts, macrophages, and endothelial cells, can either promote or hinder tumour growth. The contact and fusion of cancer cells with stromal cells can be the cause of the morphological variations between tumour cells and metastases. A genetic transmission pathway that helps malignancy progress is cell-cell fusion between cancer cells and stromal cells. Studies conducted in vivo have shown that the fusion of cancerous and healthy cells enhances the likelihood of cancer in the progeny in both intra- and interspecies fusions [39], [40]. According to one study, human genes were transferred from glioblastoma cells to healthy hamster host cells through the development of heterokaryons, resulting in hybrid offspring that expressed both human and hamster genes and gene products. This suggests that cell-cell fusion is a method of horizontal gene transfer that promotes the growth of cancer [41], [42]. Furthermore, research has shown that metastatic human-hamster hybrid tumours may transduce, transcribe, and maintain functional human genes from all human chromosomes. The heterogeneity of cancer cells, which allows them to acquire specific alterations required for survival and adaptation, is explained by the reciprocal genetic interaction between cancer cells and their stromal milieu. A crucial step in the development of cancer is the capacity of tumours to change on a cellular level, which makes it a viable target for therapeutic therapies. Surprisingly, when tumour suppressor genes are present in the hybrid cells, cell fusion can also prevent the spread of cancer. Normally, tumour suppressor genes work in cells to stop the growth of tumours by limiting cell division. Due to genes from the normal parent that prevent tumour progression, hybrids created by the union of normal cells and tumour cells might not be able to produce tumours. For instance, it's possible that 50% of malignancies contain the tumour suppressor gene P53. However, if a tumour suppressor gene is still active in a normal cell, the cell fusion event may halt the growth of the tumour. In conclusion, cell-cell fusion has a big impact on the spread of cancer cells and how heterogeneous they become [3]. For the purpose of creating specialised therapeutic approaches intended to thwart this procedure and perhaps prevent tumour spread, it is essential to comprehend the mechanisms causing cell fusion in the context of metastasis. Furthermore, the complexity and significance of cell fusion in cancer biology are highlighted by the fact that it can both promote and hinder the growth of tumours. Researchers can open the door to cutting-edge therapeutic modalities and enhance patient outcomes by figuring out the intricate processes of cell fusion in metastasis.

 

2. **Drug Resistance:** Cell fusion has significant implications, as it allows cancer cells to swiftly acquire genomic material, leading to substantial changes in cell genomes, surpassing the impact of mere mutations. The fusion of cancer cells can result in the development of new drug resistance, thereby influencing the progression and treatment of cancer. Due to the activation of enzymes that metabolise the given pharmaceuticals, increased expression of multidrug transporters, or a deficiency in drug receptors, some cancer cells have an innate resistance to certain medications[43], [44]. When distinct cell lines combine, the offspring may acquire the same level of drug resistance as the parent cells, but astonishingly, new levels of drug resistance may also develop. It can be extremely difficult to treat such double-resistant cancer cells, for example, because the union of two drug-resistant cell lines can result in a hybrid that is now resistant to both medications[45]–[47]. This phenomenon may occur at a relatively low frequency, but it plays a pivotal role in allowing rare hybrid cells to survive and give rise to tumor relapse, hampering the efficacy of therapeutic interventions. Cell fusion may also provide explanations for two current models, shedding light on the mechanisms driving cancer medication resistance. According to the first model, which is comparable to the theory of biological evolution, cancer cells adapt to their microenvironment, changing their phenotypes and giving a tiny percentage of resistant cells a chance to live and go undetected by routine tests. According to the second theory, cancer cells must have cancer stem cells (CSCs) in order to survive chemotherapy[48]. CSCs are a distinct subpopulation of tumour cells that has stem cell-like traits, such as the capacity for self-renewal and the capacity to develop into different cancer cells. Cell fusion can indeed contribute to both of these models. By facilitating rapid genetic exchange between cancer cells, fusion events can lead to the formation of subpopulations with different drug resistance capacities, enabling tumor cells to overcome the effects of chemotherapy and other treatments. Additionally, fusing with non-resistant tumor cells or surrounding tissue cells may endow the progeny with drug resistance, further contributing to tumor heterogeneity and resistance. Moreover, mitochondrial abnormalities in cancer cells may also play a role in drug resistance, as the hypoxic tumor microenvironment and impaired mitochondrial function can drive changes in cancer cell metabolism. Mitochondrial defects or hypoxia can enhance glycolytic activity and drug resistance in tumor cells. Thus, cell fusion and its potential effects on cytoplasmic exchange can provide novel insights into drug resistance from the perspective of altered metabolism. Understanding the multifaceted role of cell fusion in cancer drug resistance and metastasis is of utmost importance in cancer research and therapeutic development. The interactions between cancer cells through fusion events contribute to tumor heterogeneity and resistance, posing new challenges and opportunities for innovative approaches in cancer treatment. Efforts to unravel the mechanisms and consequences of cell fusion will undoubtedly contribute to the development of targeted therapies and improve the clinical outcomes for cancer patients.

## IV. IMMUNE-CANCER CELLS FUSION: FUSION HYBRIDS, A POTENTIAL THERAPEUTIC TARGET

1. **Macrophages and Cell Fusion:** Through cell fusion processes, macrophages have an impact on metastasis. The invasion of distant organs by metastatic tumour cells is known to occur non-randomly, with the most frequent sites of invasion being the lungs, liver, and bones. According to extensive research, the fusion of macrophages and tumour epithelial cells results in the development of hybrid cells with the ability to migrate and occupy

 

distant organs and tissues. A suggested process for metastasis involves cell fusion between bone marrow-derived cells (BMDC) and cancerous tumour cells, in which the BMDC contributes its capacity for movement and the main tumour cell contributes its proliferative capacity. Numerous studies have shown how hybrid cells, which have traits from both their epithelial and macrophage parent cells, aid in the development of metastatic cancer phenotypes[49]. Additionally, particular macrophage markers, including CD163, have been discovered in breast and colorectal malignancies and are linked to advanced tumour stages and lower survival rates. When tumour cells and macrophages fuse, hybrid cells having various macrophage features that the tumour cells did not have before the fusion are created. Phagocytic behaviour, a feature of M2 macrophages and frequently seen in malignant tumour cells, is displayed by these hybrid cells[50]. The deadliest cells within a tumour have the potential to be tumour cells that develop macrophage characteristics through cell fusion.It is still unclear how metastatic tumour cells choose to infect particular organs over others. However, it is proposed that the choice for these places as "soil" for metastatic malignancies may be explained by the presence of macrophages in particular tissues, which is controlled by the degree of bacterial exposure and the extent of damage to existing macrophages[51], [52]. Additionally, radiation therapy has been associated with increased macrophage-epithelial cell fusion, which has been linked to reduced survival in some cancer patients who have had radiation therapy.

2. **Deciphering the Elusive Mechanisms of Organ-Specific Metastasis: Fusion Hybrids Take Center Stage**: Metastasis, the spread of cancer cells to distant organs, poses a formidable challenge in cancer research and treatment. Among the intricate steps involved in this perilous journey, extravasation and adaptation to the microenvironment of distal organs are critical rate-limiting factors. While we have made progress in understanding the preparation of premetastatic niches, the underlying reasons behind the selection of specific organ sites remain shrouded in mystery. In this pursuit of knowledge, fusion hybrids—formed by the fusion of cancer cells with macrophages—emerge as intriguing protagonists, offering new insights into the enigma of organotropism. The traffic and homing of leukocytes, essential components of the immune response, are orchestrated by chemokines and cell adhesion molecules[53]. Chemokines drive chemotaxis, guiding leukocytes to specific locations, while cell adhesion molecules, like selectins and integrins, facilitate cellular adhesion and extravasation[54], [55]. Remarkably, fusion hybrids demonstrate an exceptional ability to express leukocyte-specific adhesion molecules, particularly β2 integrins[56]. Since leukocytes are the only cells that express the β2 integrins, they play a crucial role in this process. The ability to express β2 integrins, which act as a compass to direct fusion hybrids to particular organs, is a remarkable property bestowed upon fusion hybrids by the fusing of tumour cells with macrophages. Beyond β2 integrins, the fusion with macrophages induces upregulation of other adhesion molecules, adding to the fusion hybrids' prowess in organ-specific metastasis. The intriguing VLA-4, or integrin α4β1, emerges as a prominent player, interacting with vascular cell adhesion molecule -1 (VCAM-1) and facilitating firm adhesion [54].

Complex localization signals are produced by the dynamic expression of specific chemokines and integrin ligands by the local endothelium in response to tissue type and conditions, directing leukocyte populations to the exact areas and times they are required. Interestingly, fusion hybrids exhibit improved migration towards the important

 

chemokines stromal cell-derived factor-1 (SDF1) and colony-stimulating factor 1 (CSF1), which control bone metastases [57]. Although this observation was initially seen in a colon cancer cell line, it raises exciting questions about the function of fusion hybrids in targeting bone structures, especially in tumours where bone metastasis is uncommon[58], [59].

To unravel the mysteries of organotropism, the behaviour of fusion hybrids has been meticulously studied. Experimental metastasis assays in mice revealed the presence of hybrid cells in lymph nodes and spleens long after injection, hinting at their potential role in the formation of premetastatic niches. Interestingly, primary lung cancer metastasizing to the spleen challenges the traditional circulatory pattern hypothesis of organotropism, urging us to explore alternative mechanisms and players at play. As the scientific expedition delves deeper into the enigmatic world of metastasis, fusion hybrids take center stage as key players in shaping organotropism. Their ability to integrate leukocyte-specific adhesion molecules opens new avenues for understanding the intricate language of metastatic spread. With each discovery, we inch closer to deciphering the complexities of organ-specific metastasis.

3. **Unveiling the Immune Evasion Strategies of Fusion Hybrids:** Intriguingly, the prevalence of circulating fusion hybrids, surpassing conventional circulating tumor cells (CTCs), beckons us to explore whether these hybrids possess distinct immunomodulatory features, setting them apart from non-fused cancer cells[60], [61]. Immunological investigations have shed light on their intriguing resistance to specific cytokines. Transforming growth factor (TGF-beta 1-3), renowned for its regulatory influence on cellular behavior, exhibited a dose-dependent suppression of MC38 cell proliferation but proved ineffective against the resilient hybrids. Even more notably, the potent antitumor agent, tumor necrosis factor–alpha (TNF-alpha), failed to hinder the relentless growth of fusion hybrids, in stark contrast to its inhibitory impact on unfused MC38 cells [62].

Moreover, fusion hybrids display a remarkable ability to influence immune surveillance by interacting with pivotal immune cell populations in distinct ways. Upon exposure to fusion hybrids, CD4+ and CD8+ T-cells experienced a marked reduction in mitogen-induced proliferation, indicating the hybrids' potential to modulate T-cell responses. Notably, fusion hybrids induced the upregulation of FoxP3, PD-1, and CTLA4 expression in T-cells, a phenomenon absent in co-cultures with unfused lung cancer stem cells. Similarly, NK cells, the effectors of natural immunity, appeared to have their cytotoxic activity subdued when co-cultured with fusion hybrids compared to unfused lung cancer stem cells. This dampening effect may be attributed to the elevated expression of PD-1, CD39, CD73, and SIGLEC5 by the hybrids, possibly facilitating immune evasion [63].

Furthermore, co-cultivation with fusion hybrids resulted in a restrained upregulation of IFNγ, TNFα, and IL-6 production in peripheral blood mononuclear cells (PMBCs), suggesting potential resistance to innate mechanisms of tumor suppression. In conclusion, the immune evasion strategies of fusion hybrids present an intriguing facet of their metastatic behavior. Their ability to elude immune surveillance and modulation of immune cell responses raise pivotal questions for further exploration. Unraveling the mechanisms behind their interactions with the immune system may yield valuable

 

insights into novel therapeutic approaches, with the ultimate goal of counteracting their invasive potential and advancing our quest to combat metastatic cancer.

4. **Dendritic Cell-Tumor Fusion Hybrids Vaccines**: Dendritic cell-tumor fusion hybrids vaccines represent a cutting-edge approach in cancer immunotherapy. These vaccines are designed to harness the immunostimulatory properties of dendritic cells (DCs) and the tumor-specific antigens expressed by cancer cells. By fusing these two cell types, the resultant hybrid cells offer a unique and personalized vaccination strategy for activating the body's immune system against the tumor. The process of creating dendritic cell-tumor fusion hybrids vaccines involves several key steps, firstly isolation and Maturation of Dendritic Cells (DCs). Dendritic cells are derived from the patient's own blood or bone marrow and then matured and activated in vitro to enhance their antigen-presenting capabilities. Then, tumor cells are obtained directly from the patient's tumor tissue or cultured tumor cell lines. These cells carry a repertoire of tumor-specific antigens that are unique to the individual's cancer. The isolated and matured dendritic cells are then fused with tumor cells using specialized fusion methods. This process creates dendritic cell-tumor fusion hybrids that express a broad array of tumor-specific antigens on their surfaces. Once the fusion hybrids are generated, they are re-infused back into the patient as a personalized vaccine. The dendritic cell component of the fusion hybrids serves as a potent antigen-presenting cell, presenting tumor-specific antigens to the patient's immune system. This stimulates a targeted immune response, leading to the activation of cytotoxic T cells and other immune effectors that recognize and attack the tumor cells expressing these antigens[64]. A recent study has unveiled a noteworthy discovery, demonstrating that the introduction of alpha-gal in MDA-MB-231 (Gal+) tumor cells have a profound impact on the potency of a tumor/dendritic cell (DC) fusion vaccine[65]. This expression triggers the activation and maturation of dendritic cells, leading to increased production of the immune-stimulating cytokine IL-12. Moreover, the vaccine induces the proliferation, activation, and cytokine production of T cells, integral components of the immune response. The implications of this heightened immunogenicity are remarkable. The vaccine exhibits exceptional specificity, displaying superior cytotoxicity specifically against MDA-MB-231 tumor cells, without affecting other tumor cells or normal cells. This precise targeting is crucial for minimizing side effects and maximizing vaccine effectiveness. Beyond its selectivity, the vaccine's effects extend to in vivo settings. When administered to mice with tumors, the a-gal-expressing MDA-MB-231 (Gal+)/DC vaccine triggers robust systemic immune responses. These responses effectively inhibit tumor growth and significantly prolong mouse survival. While dendritic cell-tumor fusion hybrids vaccines show great promise in cancer immunotherapy, several limitations should be considered:

    - **Individualized Approach**: The process of generating personalized vaccines for each patient can be time-consuming and labor-intensive. It requires isolation, maturation, and fusion of dendritic cells with tumor cells from each patient, which may limit the scalability of this therapy for widespread use.
    - **Heterogeneity of Tumor Antigens:** Tumors are genetically diverse, and the repertoire of tumor antigens can vary among patients and even within the same tumor. Consequently, the efficacy of dendritic cell-tumor fusion hybrids vaccines may vary depending on the range and abun dance of tumor-specific antigens present in each patient's tumor.

 

- **Immunosuppressive Tumor Microenvironment:** In some cases, tumors create an immunosuppressive microenvironment that hinders the activation and function of immune cells, including dendritic cells. Overcoming these immunosuppressive mechanisms is critical to achieving robust and sustained anti-tumor immune responses.
- **Clinical Outcomes and Long-Term Effects:** While early-phase clinical trials have shown promising results, larger and more comprehensive studies are needed to determine the long-term safety, efficacy, and durability of dendritic cell-tumor fusion hybrids vaccines. The optimal combination of this approach with other immunotherapies or conventional treatments also requires further investigation.

## V. FUTURE PERSPECTIVES

Immunotherapy has emerged as a groundbreaking approach in cancer treatment, leveraging the body's immune system to target and fight cancer cells effectively. In the context of cell fusion and its implications in cancer biology, immunotherapy takes on even greater significance. The process of cell fusion, which involves the merging of cancer cells with other cell types, plays a crucial role in tumor progression and metastasis. By understanding the mechanisms of cell fusion, researchers have gained valuable insights into how cancer cells interact with the surrounding microenvironment and evade the immune system.

As we look to the future, the study of cell fusion holds immense promise for advancing cancer research and therapy. One of the most exciting prospects is the development of targeted therapies aimed at disrupting or preventing cell fusion events. By doing so, we can impede the growth and spread of cancer, leading to more effective treatments. Additionally, fusion hybrids resulting from cell fusion could serve as specific targets for novel anti-cancer drugs, opening up new possibilities for drug development. Moreover, cell fusion has significant implications in cancer immunotherapy. Dendritic cell-tumor fusion hybrid vaccines, for instance, have shown promising results in stimulating anti-tumor immune responses. Harnessing this knowledge could lead to the development of improved cancer vaccines and immune-based therapies. Understanding the tumor microenvironment and its role in cell fusion is another crucial area of research. By targeting the stromal components involved in fusion events, we may develop therapies that not only inhibit cell fusion but also disrupt the tumor's support system, hindering its growth. Furthermore, the relevance of cell fusion extends beyond cancer, offering potential insights into other diseases. This opens up new avenues for therapeutic interventions that go beyond cancer treatment. As we progress, the possibility of artificially inducing cell fusion may pave the way for innovative immunological treatments and could be explored further in the future. However, it is essential to recognize that translating these findings into practical clinical applications requires the implementation of well-designed clinical trials and careful consideration of ethical implications.

## VI. CONCLUSION

In conclusion, cell-cell fusion is a fundamental biological process with diverse implications in both normal physiological functions and cancer biology. This intricate process plays critical roles in various developmental processes, tissue homeostasis, and regeneration

 

in various organs. However, it also extends its influence to cancer biology, where both normal and cancerous cells exploit cell fusion to promote malignancies and contribute to tumor evolution. Cell fusion allows the combination of genetic and phenotypic properties of parental cells, leading to the formation of hybrid cells with unique characteristics inherited from both parent cells. In cancer, fusion events between cancer cells and immune cells like macrophages can result in hybrid cells with dual tumoral proliferation and immune cell mobility properties, facilitating metastatic dissemination. Furthermore, cell fusion introduces genetic and transcriptomic reshuffling, leading to the acquisition of new properties and potential drug resistance in hybrid cells. Cell fusion significantly influences cancer progression and metastasis. The fusion of cancer cells with stromal cells contributes to organ-specific metastasis and facilitates the formation of premetastatic niches. Moreover, fusion hybrids exhibit distinct immune evasion strategies, potentially enhancing tumor survival and resistance to immune surveillance. The presence of fusion hybrids in the circulation offers new possibilities for cancer diagnosis and monitoring, potentially serving as a biomarker for disease progression. Understanding the mechanisms of cell fusion and its implications in cancer biology has paved the way for innovative therapeutic approaches.

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