Journal of Cellular and Molecular Immunology

Kloc M, J Cell Mol Immunol. 2026;5(1):17-22.

Commentary

Syncytia in disease – an overview

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Received date: October 06, 2026
Accepted date: October 15, 2026

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Abstract

Syncytia arise from cell fusion or incomplete cytokinesis of a founder cell. Naturally occurring syncytia are common in gametogenesis, development, and many differentiated tissues. Syncytia also form during pathologic conditions such as microbial infections, inflammation, and cancer. In this short commentary, we discuss the examples of cell fusion with a focus on pathological syncytia.

Keywords: Syncytium, Cell fusion, Coenocytes, Multinucleated giant cells, Bacteria, Virus, Nematode, Diseases

Overview of Syncytia Formation

Current use of the term syncytium is very imprecise and includes at least three different categories of cells [1–5]. One category is the true syncytia that derive from the fusion of two or more independent cells. Fusion between identical cells creates a homotypic syncytium, while fusion between different cell types creates a heterotypic syncytium. The nuclei of fusing cells may also fuse to form a homotypic or heterotypic polypoidal synkaryon, or remain separate within the common cytoplasm, forming a multinucleate syncytium (**Figure 1**). The second category is the coenocyte, any multinucleate cell formed by repeated nuclear divisions within a common cytoplasm. Examples include multinucleate cells of algae, slime molds, fungi, and invertebrate embryonic blastoderm (**Figure 1**). The third category is the cell cluster derived from incomplete divisions of a founder cell. The examples are invertebrate and vertebrate germ cell cysts/nests (**Figure 1**). For simplicity, in the further text, we will used the general term syncytium for all these categories. In some instances, all nuclei of the multinuclear syncytium become temporally, structurally, and molecularly synchronized as dictated by the common cytoplasm [1]. However, in some cases, the nuclei retain their individuality. Studies of the multinuclear fungus *Ashbya gossypii* showed that syncytial nuclei retain autonomy in transcription and cell cycle. The transcriptional activity of individual nuclei dictates the properties of local cytoplasm in the syncytium [2]. Another study of the same fungus showed that nuclei sharing the same cytoplasm but differing in cell-cycle stage use cytoplasmic microtubules to establish autonomous sub-cytoplasmic domains with different molecular signaling properties [3]; (**Figure 1**).

Besides syncytia described above, there are also functional syncytia, such as cardiac muscle, in which individual cells connected by the gap junctions act in unison and behave as a single functional unit [6], or the functional syncytium of the gallbladder, where smooth muscle cells, interstitial cells, and neurons function together to assure electrical rhythmicity and gallbladder motility [7].

Mechanism of Cell Fusion

Many excellent reviews describe the mechanisms of cell membrane fusion with viruses and between cells. Although a detailed description of this subject is beyond the scope of this commentary, in short, fusion of the viral envelope (acquired from the cell membrane) with the target cell membrane and fusion between the membranes of neighboring cells follow the same basic processes and mechanisms. The first obstacle to cell fusion is the energetic barrier of the so-called hydration force, a very strong short-range repulsive force caused by water molecules bound to the hydrophilic groups of membrane lipids. Hydration-force repulsion grows exponentially as the distance between

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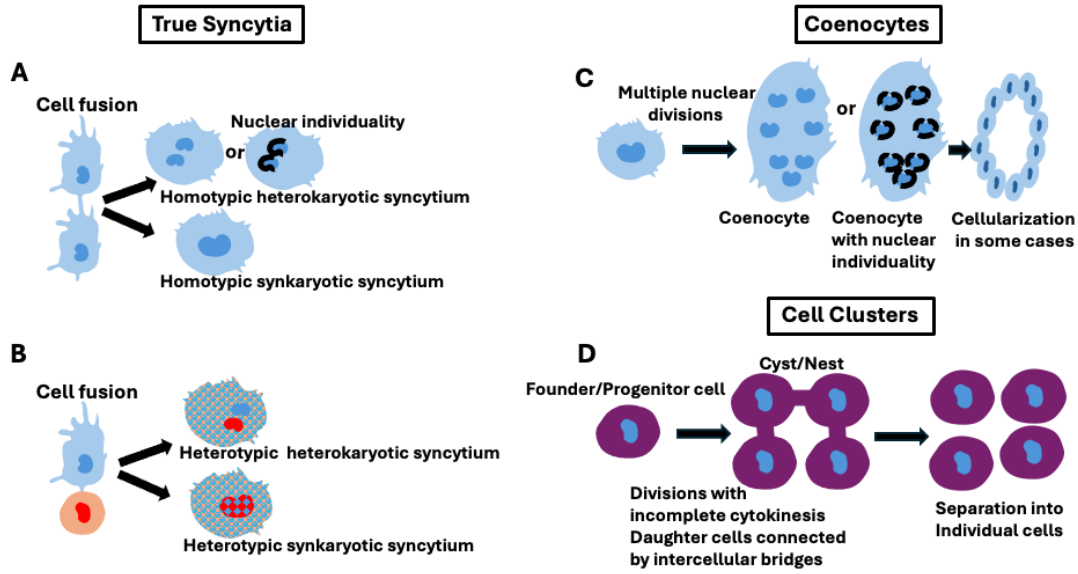

Figure 1. Types of syncytia. A) The true syncytia derived from the fusion of identical cell types creates the homotypic syncytium with unfused or fused nuclei (synkaryon). The nuclei of the syncytium either synchronize by inhabiting the common cytoplasm or become surrounded by cytoskeletal elements that separate them from the syncytial cytoplasm, retaining individuality in cell-cycle and transcriptional activities. **B)** The true syncytium derived from the fusion of different cell types creates a heterotypic syncytium with unfused or fused polyploid nuclei (synkaryon). **C)** Coenocyte is a cell with many nuclei embedded in common cytoplasm, formed by the multiple nuclear divisions without cytokinesis. The nuclei either become synchronized or retain individuality. In some cases, such as the embryonic blastoderm of *Drosophila* or developing plant endosperm, the coenocyte eventually culturalizes into separate mononuclear cells. **D)** Cell clusters (cysts/nests) of daughter cells connected by the intercellular bridges form by a series of divisions of the founder (progenitor) cell with incomplete cytokinesis. In most cases, such as animal gametogenesis, the cyst eventually separates into individual cells (gametes). Some drawings used in this figure were adapted from images at Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

cells decreases. Normally, such strong energetic barrier prevents the accidental fusion between the neighboring cells. Overcoming this energetic barrier to allow close apposition of membranes during cell fusion requires a massive amount of energy. Additionally, fusing membranes bend (form the curvature that initiates fusion), and overcoming membrane resistance to bending also requires a lot of energy. Viruses and eukaryotic cells have many specialized proteins, called fusogens, that use the free energy released during their conformational changes to overcome these energetic barriers, allowing membrane fusion. The fusogen behaves like a compressed spring, storing energy in its high-energy conformation. In the initial, pre-fusion conformation, the fusogen is in a temporary high-energy state. Receptor binding, or another trigger, converts fusogen into a stable, lower-energy post-fusion conformation, and the energy released during this conformational change is used for membrane bending and fusion (**Figure 2**) [8,9].

Naturally Occurring Syncytia

In most animals, male and female gametogenesis (spermatogenesis and oogenesis) proceed through a germline cyst stage in which daughter cells derived from the incomplete division of a primordial germ cell are connected by intercellular bridges. These bridges are temporary, and in both invertebrates and vertebrates, at the final stage of oocyte and spermatocyte formation, they break, releasing the individual, fully formed germ cells (**Figure 1**) [10–13]. A naturally occurring syncytium in animal development is the syncytial blastoderm of an early embryo, composed of multiple nuclei embedded in a common cytoplasm, for example, in arthropods, that arises from rapid nuclear divisions of the zygotic nucleus without cytokinesis (**Figure 1**) [14,15]. Another naturally occurring syncytium is the syncytiotrophoblast of the mammalian placenta, which arises from the division of mononuclear progenitor cells (cytotrophoblasts) and the subsequent fusion of daughter cells into a syncytiotrophoblast containing billions of nuclei embedded in a common cytoplasm [16,17]. Many other naturally occurring syncytia are present in various tissues and organs. Examples include skeletal muscle, formed by the fusion of embryonic myoblasts into multinuclear muscle fibers [18], or bone-resorbing multinuclear osteoclasts formed by the fusion of hematopoietic progenitors from the bone marrow [19]. Outside the animal kingdom, natural syncytia occur in fungi [20], algae [21], slime molds [22], and plants [23].

Pathogen Induced Syncytia

Many types of viruses and bacteria induce host cell fusion and syncytia formation. The main purpose of pathogen-mediated fusion between infected and uninfected cells is to enable direct transmission of the pathogen between cells while evading host immune detection and repurposing the syncytium's amplified transcriptional and translational machinery to produce large quantities of new pathogens [9,24–27]. Below are several examples of viruses that induce syncytia formation. Respiratory syncytial virus (RSV) and human parainfluenza virus 3 (HPIV3), which cause respiratory tract

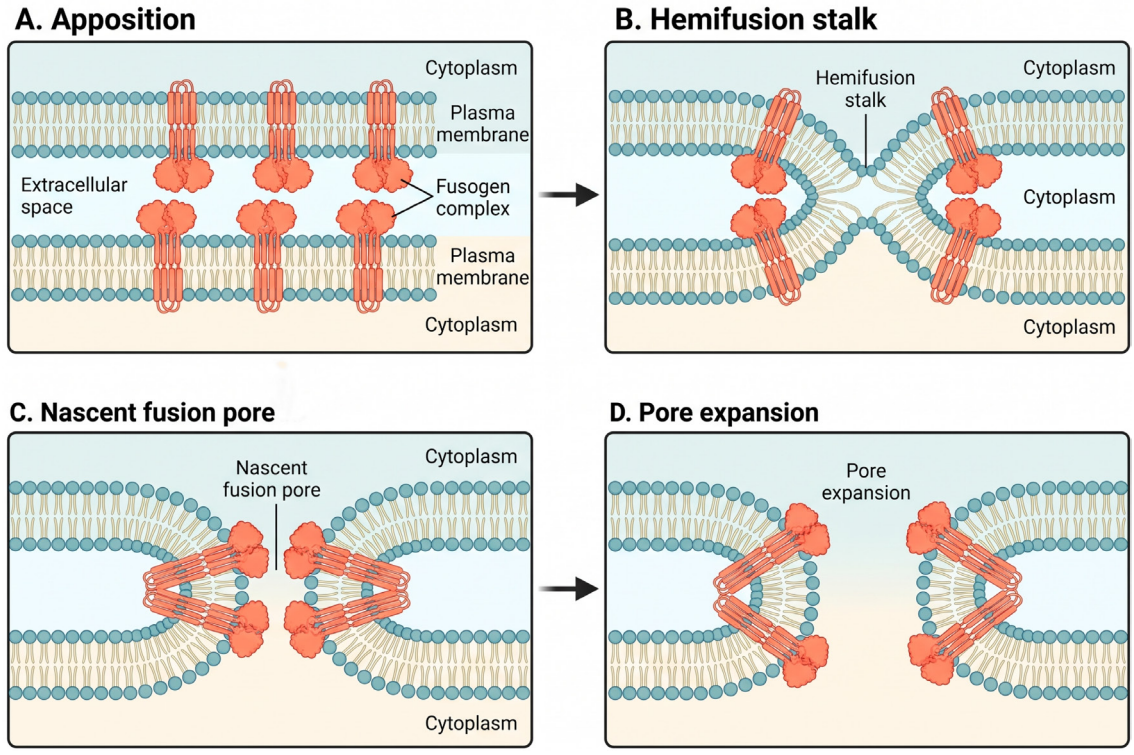

Figure 2. Fusogen-mediated cell membrane fusion. A) Membranes of two cells are brought into proximity. Transmembrane fusogen complexes embedded in membranes overcome electrostatic repulsion and establish membrane-membrane contact. The fusogen behaves like a compressed spring, storing energy in its high-energy conformation. When the initial, high-energy pre-fusion conformation of the fusogen is converted (by various triggers, such as receptor binding) into a lower-energy post-fusion conformation, the energy released during this change is used for membrane bending and fusion **B)** Fusogen-driven perturbation of the lipid bilayer creates a hemifusion stalk intermediate. **C)** Resolution of the hemifusion ruptures the membrane bilayer and forms a nascent fusion pore. Fusogens within a freshly rebuilt membrane bilayer provide a radial force that stabilizes the pore's high-energy membrane curvature, preventing nascent pore collapse and membrane resealing. **D)** Expansion of the fusion pore results in the continuity of two merging cytoplasms and syncytium formation. The figure was created in BioRender., Kloc, M. (2026) https://BioRender.com/rnb51id.

infection, pneumonia, and bronchitis, mediate fusion of infected airway epithelial cells through the viral envelope surface glycoprotein (also called the F Protein or Fusion Glycoprotein), which allows viral envelope fusion with the host cell membrane during infection and, when expressed on infected cells, mediates cell fusion and multinucleated syncytia [28–30]. Measles virus (MeV), which causes an acute increase in body temperature and skin rash, uses two envelope glycoproteins, hemagglutinin (H) for binding to the cell membrane and F protein for fusion with the cell membrane during infection and for cell-to-cell membrane fusion of epithelial cells, B cells, and other cells of lymphoid tissues to produce multinucleated giant cells (MGCs, sometimes known as Warthin-Finkeldey cells [31,32]. SARS-CoV-2 virus uses its spike fusion protein to induce pneumocyte syncytia in the lung [25,33], and HIV virus uses HIV-1 envelope glycoprotein I (Env) for entry and induction of syncytia between immune cells (T cells and macrophages) [34,35].

Bacteria in the pseudomallei group of *Burkholderia* species (endemic to subtropical and tropical regions and causing melioidosis and glanders in humans and animals) are the only bacteria known to induce cell–cell fusion directly. Unlike viruses, they do not use typical viral fusogens but induce host cell fusion through different mechanisms. *Burkholderia* species, which spread between host cells by inducing cell–cell fusion, use bacterial motility and the type VI secretion system-5 (T6SS-5) to induce cell fusion. Bacteria moving within the host cell push on the host cell membrane, forming a protrusion that extends into the uninfected cell. This protrusion expresses the TGSS-5 system proteins VgrG5 and TagD5. Studies suggest that VgrG5 and TagD5 secreted within the membrane protrusions act locally to promote membrane penetration, deformation, and fusion [26,36].

Other microorganisms, such as *Microsporidia* (unicellular organisms closely related to fungi), obligate intracellular parasites with over 1,000 species infecting nearly all animal species and humans [37], can cause dramatic enlargement of host cells, producing so-called xenomas. Some microsporidia species induce enlarged cells with a single, highly modified nucleus, while others may induce multinucleated coenocytes or syncytia [37–39]. Studies of various microsporidia species infection in *C. elegans* showed that microsporidia can fuse muscle cells, intestinal cells, hypodermis, and epidermis. Further studies are needed to determine whether fusion requires fusogens or whether microsporidia moving through neighboring cells breaks membranes, causing cell fusion [40].

Syncytia can be also induced by the multicellular parasites such as nematodes. One of the best-described examples is the formation of syncytial cysts in plant roots by cyst nematodes. Nematodes in the genera *Globodera* and *Heterodera* fuse hundreds of root cells and endoreduplicate their DNA, forming the so-called feeding cyst. They trigger local cell wall dissolution, causing hundreds of neighboring root cells to fuse into one giant, nutrient-rich syncytium. In contrast, *Meloidogyne* induces coenocytic, multinucleate giant cells within plant vascular tissue. These nematode-induced syncytia feed the parasite's juveniles and adults. Secretions from the nematode's secretory glands enable movement through neighboring root cells and alter host cell signaling, cell-cycle progression, and structural programs [41,42]. A feeding cyst can contain over a hundred cells whose walls are locally dissolved, allowing protoplast fusion. A cocktail of cell wall-modifying and degrading enzymes produced by the nematode allows it to migrate through cell walls. In contrast, during syncytium development, the plant uses its own modifying and degrading proteins [43].

Multinucleated Giant Cells

Many pathogens, in addition to causing direct fusion between infected and non-infected cells, induce the innate immune response and the formation of multinucleated giant cells (MGCs) through fusion of myeloid-origin immune cells such as monocytes and macrophages. Many reviews have described macrophage fusion and the signaling pathways involved in MGC formation in detail [44–46]. MGCs can also be induced by foreign objects and inflammatory processes. Depending on the inducing agent, MGCs have several subtypes.

Foreign body giant cells (FBGCs) are induced by chronic inflammatory reactions against foreign objects such as implants and non-infectious materials. If the foreign object is too large for macrophage ingestion and phagocytosis, macrophages will fuse into a giant cell with "a hope" that a giant cell can handle larger object removal and degradation. FBGCs reach 1000 µm in size (a single macrophage is usually~ 50 µm) and contain hundreds of nuclei embedded in a common cytoplasm. When a foreign object enters the body, it causes tissue injury and deposits blood clots and signaling molecules (chemokines, cytokines, etc.), which recruit immune cells such as macrophages to the object's surface. Over time, macrophages fuse into gigantic FBGCs. In addition to ingesting and destroying larger objects, FBGCs release reactive oxygen species (ROS) and matrix metalloproteases (MMPs) to destroy the foreign objects extracellularly [44].

Langhans' giant cells (LGCs), derived from the fusion of macrophages, are associated with infectious and non-infectious granulomas, a tightly packed aggregate of immune cells trying to separate a pathogen or foreign object from the rest of the body. They usually contain ~20 nuclei arranged at the cell periphery. The most studied are LGCs formed in *Mycobacterium tuberculosis* infection. Although they cannot destroy the pathogen, they isolate it and prevent its spread, and they produce pro-inflammatory cytokines and chemokines that attract other immune cells. LGCs also form in non-infectious granulomas, such as inflammatory disease sarcoidosis, and within tumors, where they may help clear cancer cells [44,45,47,48]. These different types of MGCs often vary in morphology. For example, typical LGCs have multiple nuclei arranged at the cell periphery in a horseshoe shape, whereas in FBGCs the nuclei are either randomly distributed in the cytoplasm or aggregated centrally. Currently, it is unknown how, or whether, the specific pattern of nuclear distribution relates to specific cell functions.

Multinucleated giant cells are also associated with aging and senescence. They are a common feature in arteriosclerosis and giant cell arteritis (GCA) in vascular aging. The inflammatory environment of aging vessels induces macrophage recruitment and fusion into MGCs that, by overproducing proteolytic enzymes, disrupt vessel wall integrity. MGCs are also common in aging human ovaries, where they may digest large fibrotic regions or remove cell debris created by multiple ovulatory cycles [49–51].

Cell Fusion in Cancer

A vast literature documents cell fusion in cancer. One example is polypoid giant cancer cells (PGCCs). PGCCs can either form through the cell cycle- and DNA replication- defects that create polyploid cell with a single nucleus or through the fusion of two or more cells creating the multinuclear PGCC [52]. Some PGCCs have stem cell-like properties that promote cancer spread, metastasis, and resistance to anticancer therapies and their progeny can vary in genome organization, plasticity, and proliferative features [53,54]. Many tumors have a unique population of tumor-associated macrophages (TAMs) that either destroy cancer cells or promote them by creating the immunosuppressive environment [47,55,56]. When immotile cancer cells fuse with TAMs (which are, like all macrophages, inherently motile) they can acquire motility and metastatic properties [49]. Another example of cell fusion in cancer is the fusion of tumor cells (T) with normal cells (N) to form TN hybrids that contribute to tumor growth and cancer progression [57].

Therapeutic Approaches

Many studies identified fusion proteins as potential targets for fusion-modifying therapies. Some therapies target fusion events in cancer [54], while others target cell fusion events in inflammatory diseases and viral infections. For example, several therapies address erosive inflammatory arthritis and metabolic bone diseases, which are driven by increased fusion-dependent formation of bone-resorbing osteoclasts. Osteoclast fusion during osteogenesis depends on the dendritic cell-specific transmembrane protein (DC-STAMP), which is present in monocytes, macrophages, and dendritic cells, the precursors of osteoclasts. Studies identified DC-STAMP-high human monocytes with a greater osteoclastogenic potential. They developed a DC-STAMP antibody that blocks osteoclast formation and has potential as a therapeutic agent in inflammatory arthritis [58]. So far, no clinically approved therapy prevents or targets cell-to-cell fusion in human diseases. The only existing anti-fusion therapies target virus-related fusion. An example of an FDA-approved anti-fusion intervention is the drug Enfuvirtide (brand name Fuzeon) for the treatment of HIV-1 infection in humans. Enfuvirtide is unique among approved antiviral medications because it inhibits HIV-1 gp41 (the HIV-1 transmembrane glycoprotein), blocking fusion-dependent entry of HIV-1 into host cells [59,60]. Fuzeon was approved for clinical use in 2003, but in 2025 it was discontinued due to the development of newer drugs targeting different stages of HIV entry, such as FDA-approved for patient use in 2018 Ibalizumab (brand name Trogarzo), a humanized monoclonal antibody that targets the CD4 receptor [National HIV Curriculum; https://www.hiv.uw.edu];

An extensive review of vaccines and therapeutic agents against respiratory syncytial virus (RSV), which causes respiratory tract infection, lists anti-RSV drugs, including those (Presatovir, Ziresovir, Sisunatovir, and Rilematovir) that inhibit viral fusion by targeting the RSV F class-I fusion proteins [61]. Among these drugs, Ziresovir was approved in February 2026 for Phase II clinical trials, and Sisunatovir received FDA Fast Track designation in 2021 for the treatment of patients with serious respiratory syncytial virus (RSV) infection.

In summary, cell fusion and syncytia formation are vital for natural and pathological biological processes such as fertilization, placenta and tissue formation, repair and regeneration, immune defense, and pathogen spread. Further studies of these subjects will not only deepen our basic knowledge but also help fight infectious and noninfectious diseases by preventing nonbeneficial cell fusion.

Funding

Not applicable.

Confect of Interest

Author does not have any conflict of interest.

Acknowledgments

The author acknowledges JC Walter Jr.'s support to the Houston Methodist Transplantation Center. Some drawings used in the **Figure1** were adapted from images at Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/) and **Figure 2** was created in BioRender., Kloc, M. (2026) https://BioRender.com/rnb51id.

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