Cells Fusion

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Contributor: Thomas Dittmar

The biological phenomenon of cell fusion remains a mystery. Even though it is mandatory for several physiological and pathopyhsiological processes considerably less is still known how the merging of two (and more) cells is regulated. Cells are not fusogenic per se. They first have to be converted into a pro-fusogenic state and have to re-enter to a non-fusogenic state after hybridisation. Likewise, different cell fusion mechanisms have been developed during evolution depending on different proteins and different membrane merging strategies. This entry gives a brief overview about those molecules and conditions that direct cell fusion.

Keywords: Cell fusion ; aneuploidy ; cancer ; heterokaryon ; tissue regeneration ; synkaryon

1. Introduction

Although different physiological processes, such as fertilization, placentation, myogenesis, osteoclastogenesis, and tissue regeneration, depend on cell fusion, the mechanism by which two (or more) cells hybridize is still not well understood [1][2][3][4]. On the one hand, cell fusion is a tightly regulated process that can be subdivided into five steps: i) priming, ii) chemotaxis, iii) adhesion, iv) fusion, and v) postfusion [5].

2. How Do Cells Fuse with Each Other?

Cells are not fusogenic per se, so they have to adopt a pro-fusogenic state first in order to fuse with other cells (“priming”). Subsequently, they have to get in close contact with each other (“chemotaxis” and “adhesion”) before they can merge plasma membranes (“fusion”). Finally, they have to return to a non-fusogenic state after the fusion process (“post-fusion”). Several proteins, such as chemokines, cytokines, proteases, adhesion molecules, transmembrane proteins or proteins that are mandatory for actin remodeling, have been identified so far that mediate distinct steps in this cell fusion cascade. However, it remains to be elucidated how cytokines, such as interleukin-4 (IL-4) or receptor activator of NF-kB ligand (RANKL), or proteases, such as matrix metallopeptidase 9 (MMP-9), are exactly involved in the process of cell fusion (for review see [1][2][5]).

In addition, different cell fusion mechanisms have been developed during evolution. For instance, the fusion of trophoblasts to syncytiotrophoblasts is chiefly regulated by Syncytin-1 and -2, which are transmembrane proteins of retroviral origin [6][7]. Syncytin-1 and -2 are still the best characterized cell fusion mediating proteins in humans, and they might also be involved in human osteoclast fusion [8] and in the fusion of cancer cells with endothelial cells [9][10] or mesenchymal stem cells [11]. In contrast, fusion of myoblasts to multinucleated myofibers depends on remodeling of the actin cytoskeleton and formation of podosome-like structures, which penetrate the target cell, thereby causing the merging of plasma membranes [12][13]. Likewise, several proteins, such as MMP-9, E-Cadherin, Syncytin-1, CD200, dendrocyte expressed seven transmembrane protein (DC-STAMP), osteoclast stimulatory transmembrane protein (OC-STAMP), CD44, and P2X7, have been identified that play a role in macrophage fusion (for review see: [1][2][4]). It is also known that the expression of these proteins is induced by cytokines, such as IL-4 and RANKL [14][15][16][17][18], suggesting that these factors are likely involved in the transition of macrophages from a non-fusogenic to a pro-fusogenic state. Nonetheless, the detailed process of macrophage fusion remains unclear.

Numerous studies further showed that the frequency of cell fusion events was increased upon acute tissue damage or chronic inflammation [19][20][21][22][10][11][23][24][25][26], which is plausible with regard to efficient BMSC-based and cell fusion-mediated tissue regeneration. BMSCs not only have to be converted into a pro-fusogenic state for subsequent hybridization with target cells but also have to be recruited to the site of tissue damage. In this context, it has been shown that the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) might also be a mediator of cell fusion. Osteoclastogenesis [17][25][26], as well as the fusion of cancer cells with endothelial cells [10][27], mesenchymal stem cells [11], or breast epithelial cells [23][24][28] can be induced by TNF-α. Some data revealed that TNF-α could mediate fusion due

to induction of MMP-9 expression [24][26], which plays a role in osteoclastogenesis and giant cell formation [26][29]. Hence, it might be assumed that TNF-α could be involved in cell fusion due to induction of pro-fusogenic proteins and/or in an overall conversion of cells into a pro-fusogenic state.

In addition to inflammation-induced BMSC-based cell fusion events, two studies revealed that cell fusion events could also occur in the absence of tissue damage and inflammation [21][30]. Using a parabiotic model (a green fluorescent protein (GFP) mouse and a ROSA/β-gal mouse were surgically joined), administration of an anti-inflammatory drug cocktail was found to promote cell fusion-derived GFP/β-Gal positive cells, which were found in approximately 5% of the intestinal crypts of ROSA/β-Gal mice [21]. Likewise, noninflammation-related fusion events were found with a frequency of approximately 0.03 to 0.21% in the murine hematopoietic system [30]. Interestingly, examination of donor and host autosomal reporter genes (*h*CD46, *m*X, CD45.2, GFP, *m*Y, and CD45.1) revealed independent segregation of alleles in more than half of the fusion products, and a loss of parental markers was even observed in some cells [30]. However, despite these genetic changes, neither lineage restriction nor malignant conversion of hematopoietic cells was observed [30]. Whether this indicates that hematopoietic cells might be more tolerant to limited chromosomal sequence gains than other cells [30] remains to be elucidated.

Both viruses and exomes have also been associated with cell fusion [31][32][33][34]. In vitro and in vivo studies demonstrated that enveloped and non-enveloped viruses could cause cell fusion (so-called fusogenic viruses), thereby giving rise to bi- and multinucleated heterokaryons (a detailed overview of fusogenic viruses is found here [35]). Enveloped viruses, such as HIV, influenza virus or herpesvirus, fuse with the plasma membrane of host cells (for review see [34]) and could cause cell hybridization by acting as bridging particles. For instance, hybridomas derived from plasma cells and myeloma cells were initially generated by using inactivated Sendai virus as a fusogen [36], which has the ability to induce bi- and multinucleated cell formation in vitro and in vivo [37]. Likewise, virus-infected cells could also fuse with other cells due to the expression of viral-derived fusogenic proteins. The nonenveloped fusogenic avian and Nelson Bay reoviruses could induce cell fusion via the expression of so-called fusion-associated small transmembrane (FAST) proteins that are localized in the plasma membrane of infected cells [38]. Binucleated cell formation by fusion was also induced by the human papillomavirus 16 oncogene E5 [39].

Exosomes are a type of extracellular vesicle with a diameter of less than 100 nm, and they originate from the invagination of the lipid bilayer of multivesicular bodies in cells (for review see [40][41]). They typically contain tetraspanins (CD9, CD63, CD81, and CD82), heat shock proteins (HSC20, HSP60, HSP70, and HSP909), MHC-I and MHC-II, cell adhesion molecules (P-Selectin, αβ-integrins and annexins), and significant amounts of mRNA, miRNA, and lncRNA (for review see [40][41]). Exosomes play a crucial role in intercellular communication and the regulation of different physiological and pathophysiological conditions, whereby their payload could be delivered to target cells by endocytosis, phagocytosis or membrane fusion [41]. Duelli and colleagues demonstrated that exosomes isolated from virus-infected cells contained viral proteins and exhibited fusogenic properties, suggesting a possible role in cell fusion [31]. Miyado et al. further showed that exosomes might be involved in cell fusion by showing that sperm-egg fusion is mediated by vesicles containing CD9 that are released from the egg and interact with sperm [42]. Because CD9 is a major component of exosomes, the authors concluded that this type of extracellular vesicle was released to mediate fertilization [42].

In brief, cell fusion is a tightly regulated but not yet fully understood process. Inflammation can induce cell fusion, which would be necessary for rapid and efficient BMSC-based tissue regeneration. However, cell fusion could also occur spontaneously after being triggered by viruses and/or exosomes.

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