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Chapter 13

Targeting Intercellular Communication in Cancer Gene Therapy

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1. Introduction

Cells dedicate a considerable amount of energy and regulatory mechanisms to ensure cell-cell communication, for this biological process is an important aspect of their machinery of survival, behavior and fate within their immediate environment. For cells, communicating is vital not only because they are part of organs and tissues of which they contribute to maintaining the integrity and proper function [1-5], but also because many of their functions need to be coordinated, quantitatively fine-tuned and/or limited in space and time. Furthermore, cells make use of communication to minimize the energetic and signaling burden, whereas a single minimal signal could be amplified and propagated, as is for instance the case of gap junction-mediated transfer of pro-apoptotic signals [6-8]. Many types of intercellular communication have been studied, among which direct cell-cell interactions could be distinguished from cellular interactions via released growth factors and cytokines. Their studies have revealed a significant potential for use in cancer therapy. The importance of cell-cell communication is particularly well revealed when defects in this process result in serious diseases, as exemplified by mutations identified in many gap and tight junction proteins [9, 10].

The diversity of the types of intercellular communications (i.e. gap junctions (GJ), tight junctions (TJ), adherens junctions (AJ) and desmosomes), implicates a diversity of signaling pathways and biological functions at stake. It further emphasizes the need for cells to communicate in different ways and for different purposes: transfer of small molecules, reciprocal signaling, establishment of barriers and polarity, control of paracellular permeability and transmission of cytoskeleton-generated forces. All of these processes have been implicated in cancer development as reviewed previously for GJs [11-13], TJs [14, 15] and desmosomes [16].

In this chapter we will present an overview of how various types of direct cell-cell communication and different groups of intercellular-dependent protein interactions have been used in

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strategies of gene therapy of cancer. Important concepts and paradigms as well as successful approaches, limitations and possibilities for the future will be discussed.

2. Intercellular communication & gene therapy: The enzyme/prodrug strategy

Cancer gene therapy has since its beginnings faced a major hurdle, the inefficiency of the methods of gene delivery to target cells (i.e. transfection and infection). While attempts have later been made to identify promising alternatives, a key development was the discovery that gap junctions could provide an efficient method that, without directly reaching every cell, could transfer the cytotoxic signal originating from a limited number of target cells to their bystander neighboring cells, thus amplifying the therapeutic effect. This process has subsequently been called "bystander effect" (BE) [17]. Triggering apoptotic death process in target cells results in the transfer of the pro-apoptotic signaling molecules to other cells with which they interact via gap junction intercellular communications (GJICs), and ultimately in the demise of both cells. The BE thus plays an important role in the efficiency of cancer therapy [18]. It also impacts the therapeutic cytotoxic side effects: since high doses of drugs are not required to kill tumor cells, normal tissues may not be reached by the treatment.

3. Use of the bystander effect in the enzyme/prodrug cancer gene therapy

Gene therapy soon became the major therapeutic application of the BE in the so-called "suicide gene therapy" involving the use of Enzyme/Prodrug cytotoxic systems, whereby target cells express an enzyme that converts a prodrug into the cytotoxic active drug, which is then transferred via gap junctions to the interacting cells [19]. The general mechanism is that the active molecules are therefore transmitted to neighboring cells via GJIC and trigger their death [20]. GJIC and connexins are essential for the BE-based enzyme/prodrug therapy [21-26] (Figure 1). Different enzymes/prodrugs have been assayed among which cytosine deaminase (CD)/5-fluorocytosine (5-FC), carboxylesterase/Camptothecin, and Herpes Simplex Virus-thymidine kinase (HSV/tk)/Ganciclovir (GCV) are prominent [27]. The CD/5-FC combination is based on the conversion of the nontoxic prodrug 5-FC by bacterial or yeast enzyme cytosine deaminase into active 5-fluorouracil (5-FU) [28]. Similarly, GCV, a nontoxic purine analogue, is phosphorylated by the enzyme HSVtk and by endogenous kinases to GCV-triphosphate, which kills cells by inhibiting DNA synthesis [29] [30]. The carboxylesterase activates the prodrug irinotecan,7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11) to the active metabolite SN-38. Another combination including the uracil phosphoribosyltransferase (UPRT) of E. coli and 5-fluorouracil (5-FU), has also been used in BE-based gene therapy, along with other less known systems. UPRT is an enzyme that catalyzes the synthesis of UMP from uracil and 5-phosphoribosyl-alpha-1-diphosphate [31].

The therapeutic potential of the HSVtk and nucleosides' combination has been assayed as early as the 70's and later extended to many types of cancers both *in vitro* and *in vivo* [32-41].

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Originally tried using retroviral vectors, the same approach adapted to adenoviral vectors was later introduced and used successfully [42-44]. These and subsequent studies, all have in common the use of an efficient delivery system, mostly adenoviral, modified to improve the transduction efficiency or selectivity, in combination with an enzyme/prodrug system, most often the HSVtk/GCV, to achieve cancer cells' cytotoxicity. Virus-free delivery has also been attempted using liposomes for instance, with more or less good efficacy [45-47], but most of the studies have used viral delivery.

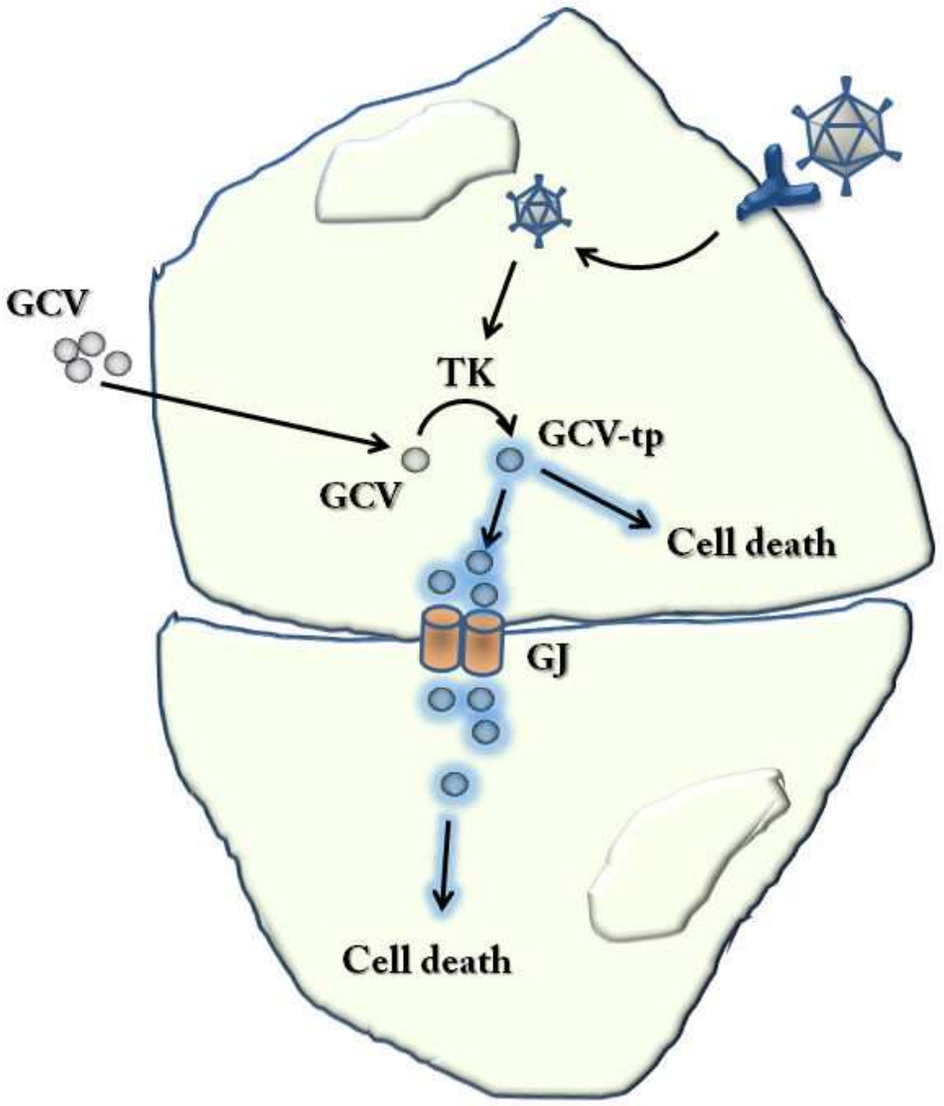

Figure 1. The enzyme/prodrug system and the bystander effect. Delivery via viral or non viral vectors of DNA sequences expressing an enzyme, here the herpes simplex virus thymidine kinase gene (TK) in the presence of the prodrug inactive substrate, here ganciclovir (GCV), results in the synthesis of the active metabolite, here GCV triphosphate (GCV-tp), which kills not only the target cell, but the neighboring bystander cell as well. This 'bystander effect' is mediated by a direct transfer of cytotoxic signals through gap junctions (GJ)-mediated intercellular communication.

3.1. Combination of oncolytic viruses and enzyme-prodrug gene therapy

Viruses are preferred vehicles for the transfer and delivery of engineered genes into host cells in gene therapy approaches. Recently, they have emerged as not only delivery vectors, but as *bona fide* therapeutic agents [74-77] (Figure 2). Oncolytic replication-competent viruses infect, replicate in and kill tumor cells. Examples abound of attempts to combine gene therapy and oncolytic virotherapy. Furthermore, the enzyme/prodrug systems have been used to improve the anti-tumor efficacy of oncolytic viruses. Early studies addressing the use of HSV vectors as oncolytic agents, showed that HSV-mediated oncolysis is enhanced by ganciclovir treatment through bystander effect [78]. A recombinant HSV (M012) was constructed to express the bacterial CD gene and was shown to enhance the prodrug-mediated anti-tumor effects after intracranial delivery in murine neuroblastoma and human glioma cells [79]. An oncolytic adenovirus modified to bear the human telomerase promoter (hTERT), was used to deliver the gene for the prodrug-activating enzyme carboxypeptidase G2 (CPG2) to tumors. The CPG2 metabolizes the prodrug ZD2767P into a cytotoxic drug and this strategy was shown to be effective in colorectal carcinomas via bystander effects and induction of apoptosis [80]. A recombinant Vesicular stomatitis virus (rVSV) encoding the CD/UPRT fusion gene was delivered intratumorally in the presence of the systemically administered 5-FU and significantly reduced growth of lymphoma and breast cancer cells *in vivo*. This effect involved three mechanisms: a strong bystander effect, the viral oncolytic activity as well as the activation of the immune system against the tumor [81]. Recombinant vesicular stomatitis virus (VSV) made to express CD/UPRT was delivered to breast cancer cells in combination with 5-fluorocytosine (5FC) [82]. An oncolytic adenovirus Ad5/3-Delta24FCU1 expressing the fusion suicide gene FCU1, which encodes a bifunctional fusion protein that metabolizes 5-FC, was found to exert significant anti-tumor activity *in vitro* and *in vivo* in a murine model of head and neck squamous cell carcinoma [83]. ONYX-015 (*dl*1520), a conditionally replicating adenovirus (CRAd) made of an E1B-55k-deleted oncolytic adenovirus and which has anti-tumor effects [84], has been combined with the CD/5-FC system and the enzyme/prodrug system involving *E. coli* nitroreductase (NTR) which can reduce nitro(hetero)aromatic compounds to hydroxylamines and amines, and both combinations showed enhanced efficacy *in vitro* and *in vivo* [85, 86]. Similarly, an oncolytic measles virus (MV) armed with the prodrug convertase, purine nucleoside phosphorylase (PNP) and the prodrug 6-methylpurine-2'-deoxyriboside (MeP-dR), was tested in a model of murine colon adenocarcinoma cells in syngeneic C57BL/6 mice and shown to have anti-tumorigenic effects after systemic delivery [87]. In spite of this available literature, many questions remain open. The factors defining the efficacy of this combinatorial therapy are not clearly identified and the strategy might not have any advantage in certain contexts. For instance, an oncolytic adenovirus, selective for the Rb/p16 pathway, killed ovarian cancer cells effectively by Tk/GCV-driven BE. However, while GCV improved the adenoviruses' antitumor efficacy over the replication-deficient virus counterpart, it did not further enhance its efficacy *in vivo*, suggesting that the prodrug strategy may not add antitumor activity to highly potent oncolysis [88].

3.2. Combined use of the enzyme/prodrug cancer gene therapy and gap junction communication restoration

Although since the beginning of the use of the enzyme/prodrug approach, it was found that the BE involves effects that do not depend on direct cell-cell interaction and are rather related to diffusible molecules released extracellularly and possibly to immune-related effects [48-51], the role of gap junctions-mediated intercellular communication (GJIC) and connexins was deemed essential [25, 26, 52-54] [55]. In light of the observed loss of connexins' expression in many cancers, the efficiency of the enzyme/prodrug approach could be limited by the ability of tumor cells to undergo GJICs between gene-transduced and bystander non-transduced cells. The levels of connexins and GJIC could modulate the impact of the bystander effect of the prodrug/enzyme systems, as shown for HSVtk/GCV *in vitro* and *in vivo* [56, 57]. This was suggested to be a reason behind the limited efficacy of the viral HSVtk/GCV delivery in many reports [58-60]. Nevertheless, many attempts have been made to bypass this limitation by restoring connexins' expression and the ability to undergo GJIC. This could be achieved either by the direct delivery of Cx-encoding vectors [61-64] or by pharmacological induction of Cx expression. The later approach involved for instance treating with DNA demethylating agents [65], histone deacetylases' inhibitors (HDACi) [66-68], ATP-sensitive potassium (KATP) channels' inhibitors [69], treatment with all-trans retinoic acid [70] or cyclic-AMP [71-73].

3.3. Applications of the enzyme/prodrug gene targeting of stem cells

Cellular vectors, including stem cells, have been used for effective gene delivery in cancer therapy. Stem and progenitor cells have been acknowledged as important for both normal and cancer homeostasis. In particular, according to the cancer stem cells' theory, tumors contain a very small sub-population of self-renewing and highly proliferating cells called cancer stem cells (CSCs), which are responsible for the tumorigenic activity [89]. Mesenchymal stem cells (MSCs), which have a strong tropism for tumor cells, are another type of stem cells of importance in cancer understanding and therapeutic targeting [90]. The use of allogeneic and hence escaping immune vigilance mesenchymal stromal cells (MSCs), sometimes called mesenchymal stem cells, as Trojan horses to deliver the enzyme/prodrug within the tumor mass is a relatively new development in gene therapy. MSCs are used as carriers of the enzyme via viral transduction, which subsequently activates the prodrug and kills not only the MSCs but their neighboring cancer cells (Figure 2). This strategy has been tested in many cancers, as illustrated by the following examples.

It has been shown that MSCs localize primarily to the perivascular environment in many organs and, when implanted or injected into animals, they show a tropism for primary tumors and metastases, and specifically for the perivascular niches within tumors [91, 92]. Based on this preferential migration, MSCs have been used as a vehicle in gene therapy strategies [93, 94]. The cytosine deaminase prodrug system has been partnered with the human MSCs and the combination increased the bystander effect and selective cytotoxicity on target tumor cells *in vitro* and *in vivo* [95-97]. Similarly, human neural stem cells (NSCs) have been successfully used to therapeutically target brain cancers. In fact, both MSCs and NSCs show high tropism for brain cancers and have been combined with the prodrug system to target brainstem

gliomas, a form of childhood central nervous system tumors with poor prognosis or medulloblastomas [98-101], and even in disseminated brain metastases of non-neuronal origins such as melanoma and breast cancer [102-104]. The success of this approach now warrants clinical trials such as the one recently started to study the feasibility of intracerebral administration of NSCs in combination with oral 5-FC in patients with recurrent high-grade gliomas [105].

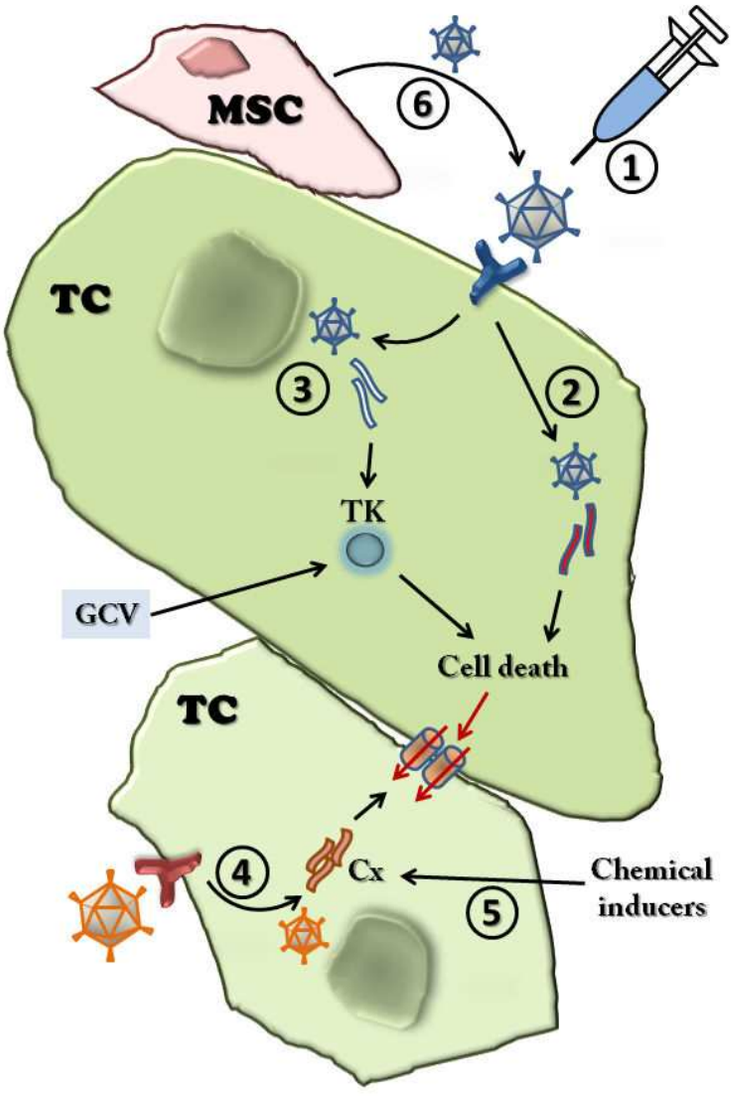

Figure 2. Different approaches of intercellular communication-based gene therapy. Tumor cells (TC) are targeted with oncolytic viruses which, in addition to their proper cytotoxic effects [1], could be combined with the bystander effect ensured by the enzyme/prodrug system, here for example the TK/GCV pair [3]. TCs are made sensitive to the bystander effect cytotoxic effects by inducing connexin (Cx) expression and the formation of gap junction intercellular communication. This is achieved by either 4) viral vectors, or 5) pharmacological inducers. Cellular delivery of the viral vectors for the enzyme/prodrug system could also be achieved using mesenchymal stem cells (MSCs) and other types of stem/progenitor cells [6].

Based on the tropism shown by neural stem cells (NSCs) for glioma cells, the herpes simplex virus-thymidine kinase (HSVtk)/GCV system has also been used in targeting gliomas [106-108]. However, for practical reasons related to the availability of cells, the use of MSCs might be more relevant clinically than the use of NSCs [109]. The system has also been tested for AT-MSCs [110] and bone marrow-derived tumor-infiltrating cells (BM-TICs) targeting of gliomas [111]. It was also proven to have a strong anti-tumor growth in medulloblastomas [112].

As discussed earlier, a major limitation to the efficacy of the therapeutic use of GJIC is the deficiency in the bystander effect due to low expression levels of connexins. Expectedly, this is also a challenge when using the prodrug/stem cells combined therapy. This can be bypassed by restoring connexin levels. For instance, GSCs showed more reduced GJIC and connexin levels than differentiated glioma cells [113]. Valproic acid (VPA) was able to upregulate Cx43 and Cx26 and to enhance the bystander effect of suicide gene therapy by human bone marrow MSCs expressing HSV-TK (MSCs-TK) [114]. In another study, the use of Bone marrow-derived stem cells (BMSCs) in combination with the (HSV-TK)/GCV suicide gene therapy of gliomas was improved by Cx43 overexpression *in vitro* and *in vivo* [115].

The MSC/Prodrug and Oncovirus/Prodrug strategies are often combined. For instance, MSCs transduced with an adenoviral vector modified to express integrin-binding motifs (Ad5lucRGD) for better transduction efficiency, and expressing thymidine kinase were able not only to kill ovarian cancer cells via bystander effect, but also support replication of adenoviruses which could result in further sustaining the effect [116].

MSCs can also act through an anti-angiogenic mechanism. They have been shown to target endothelial cells and inhibit capillary growth, establish Cx43-based GJIC with the target ECs, and to increase the production of reactive oxygen species (ROS). This effect culminates in the induction of apoptosis, thus inhibiting tumor growth in a model of melanomas [117].

3.4. The enzyme/prodrug approach in non-gap junctional communications

Curiously, unlike gap junctions, the number of studies delivering tight and adherens junctions or desmosomal proteins for cytotoxic gene therapy is limited. The adenoviral delivery of TK and E-cadherin genes improved TK/GCV cytotoxicity and antitumoral activity in pancreatic cancer cells [118].

Nevertheless, other cell-cell adhesion proteins, either or not with known links to these junctions, have been targeted in the enzyme/prodrug approach, as illustrated by the following examples. Carcinoembryonic antigen (CEA), a glycoprotein involved in cell-cell adhesion as well as cell-extracellular substrate adhesion, is a particularly prolific case. The expression of CEA in cancer cells with the exclusion of adult normal cells has been used in multiple ways to provide specificity to the Enzyme/Prodrug system. This directed enzyme/prodrug therapy, involves the generation of a recombinant plasmid, containing CEA promoter to specifically drive the expression of the enzyme/prodrug systems in CEA-expressing cancer cells [119-121]. The E. coli purine nucleoside phosphorylase (ePNP) under the control of CEA promoter sequences greatly improved the antitumor efficacy of the ePNP/MePdR killing system in

pancreatic cancer cells [122]. The use of the double system including TK/GCV and CD/5-FC, in CEA-positive lung cancer cells, resulted in enhanced cytotoxicity [123]. A CEA promoter-regulated oncolytic adenovirus vector driving the Hsp70 gene expression in CEA-positive pancreatic cancer cells was also active *in vitro* and *in vivo* [124]. Similar results were obtained by targeting suicide gene CD expression to colon cancer cells [125]. An E1A, E1B double-restricted oncolytic adenovirus, AxdAdB-3, improved the therapeutic efficacy of the HSVtk/GCV system in gallbladder cancers when directed by the CEA promoter [126]. A modification of the approach done earlier, involved the addition of four tandem-linked NF-kappaB DNA-binding sites (kappaB4) and a kappaB4 enhancer upstream of the CEA promoter, thus sensitizing colon cancer cells to the thymidine phosphorylase (TP)/ 5-fluorouracil (5-FU) or 5'-deoxy-5-fluorouradine (5'-DFUR) combinations [127]. A different way of targeted delivery of adenoviral vectors involved the generation of a bispecific adapter protein (sCAR-MFE), consisting of a fusion of the ectodomain of the coxsackie/adenovirus receptor (sCAR) with a single-chain anti-CEA antibody (MFE-23) [128]. A specific CEA RNA-targeting ribozyme was developed and used for selective delivery of HSVtk/GCV cytotoxic activity, into CEA-expressing cancer cells [129].

A high affinity antibody for Neural cell adhesion molecule 2 (NCAM2), a cell-cell adhesion molecule, which is also capable of cell-extracellular matrix adhesion, was useful in increasing transduction efficiency of a fiber-modified adenoviral vector Adv-FZ33 in prostate and breast cancers, and restoring sensitivity to the UPRT/5-FU system in previously resistant cells [130]. An Adenoviral vector incorporating an IgG Fc-binding motif (Z33) from the Staphylococcus protein A (Ad-FZ33) combined with tumor-specific anti-EpCAM (epithelial cell adhesion molecule) antibodies improved the viral transduction and the growth suppression of biliary cancer xenografts in nude mice in response to the UPRT/FU combination in human biliary cancers [131]. A similar approach used the enzyme/prodrug system comprised of the enzyme carboxylesterase (CE) and its substrate the anticancer agent CPT-11 (irinotecan or 7-ethyl-10[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin). An adenoviral vector Ad.C28-sCE2 containing a fusion gene encoding a secreted form of human liver CE2 targeted to EpCAM was efficient in colon cancer spheroids [132]. As for CEA, the validation of the use of the EpCAM promoter to target the HSVtk/GCV therapy to cancer cells has been performed [133].

4. Gene therapy using bystander effect-independent intercellular communications

The prominence of BE-based gene therapy in the literature should not eclipse the importance of other intercellular communications which do not involve the BE as candidates for gene therapy. These include in addition to a GJIC-independent role of connexins, other types of cell-cell junctions as well as other types of protein-protein (ligand-receptor) interactions who depend on cell-cell interactions for their functions. Although to different extents, all these intercellular events have proven very amenable to gene therapy strategies.

4.1. GJIC-independent effects

The key players in the BE are connexins, the building blocks of gap junctional intercellular communication (GJIC) [23, 134, 135]. Even though the effectiveness of restoring Connexins' and GJIC's levels has traditionally been associated with the bystander effect in gene therapy, it has become clear that many functions of connexins, could be dissociated from both GJIC and the bystander effects [136-138] [139] [140] [141]. In this case, delivery of Cxs-encoding vectors could be used as a gene therapy approach, regardless of the use of enzyme/prodrug systems. However, future use of such application requires a better understanding of the non GJIC-related functions of these proteins, including their interacting partners and the mechanisms of their subcellular localization.

4.2. Desmosomes, adherens and tight junctions in gene therapy

Adherens junctions and their related desmosomes, as well as tight junctions are essential types of cell-cell adhesion in both normal homeostasis and tumor progression [142-148]. Claudins are key tight junction proteins whose expression is deregulated in many cancers [146, 149]. Claudins CLDN3 and CLDN4 function as receptors for the Clostridium perfringens enterotoxin (CPE) produced by the bacterial Clostridium type A strain, resulting in cell death. A gene therapy application based on CPE gene transfer-mediated cytoxicity has been achieved but, as expected, was limited to CLDN3- and CLDN4-overexpressing tumors [150]. SiRNA-mediated silencing of the expression of Epithelial Cell Adhesion Molecule (EpCAM or CD326), a cell-surface protein involved in tight junctions and metastasis in colon, breast and other epithelial carcinomas, was effective in decreasing the growth of breast cancer cells [151]. The same approach was used with an antibody against the carcinoembryonic antigen (CEA) in gastric cancer [152]. In fact, CEA has been extensively targeted in gene therapy approaches in different ways. A recombinant form of the oncolytic measles virus Edmonston strain (MV-Edm) changed to express CEA, demonstrated high cytotoxicity towards hepatocellular carcinoma cells *in vitro* and *in vivo* after either Intratumoral or intravenous delivery [153]. The cell adhesion molecule CECAM1, or carcinoembryonic antigen-related cell adhesion molecule 1, has served in an adenoviral gene therapy targeting prostate cancer cells and showed tumor suppressor activities *in vivo* [154].

It is noteworthy that even when targeting these cell-cell communications could not be directly performed or if it fails to affect tumor growth, there is no doubt about their impact on gene therapy applications. Cell-cell communications could indeed constitute a source of impediment to gene therapy, by constituting physical barriers to tumor targeting with oncolytic viruses *in vivo* [155] [156, 157]. This is particularly important in tissues such as the lung, intestine and reproductive system which show natural mechanisms of resistance to viral infection and might thus be less amenable to viral gene delivery. In fact, many junction proteins have been shown to be receptors for many viruses. The protein originally known as coxsackie-adenovirus receptor (hCAR), which was used in adenoviral-based gene therapy for cancer before realizing that it is a component of epithelial tight junctions [158, 159], affects the efficacy of the adenoviral gene therapy approach [160, 161]. Desmoglein-2 (DSG-2), a desmosomal adhesion glycoprotein, is a receptor used by adenoviruses

Ad3, Ad7, Ad11 and Ad14, which subsequently results in epithelial-to-mesenchymal transition-like changes and transient opening of intercellular junctions, a finding that could have an impact on the adenoviral gene delivery to normal or cancer cells [162, 163]. Adherens junction proteins Nectin-1 and -2 are entry receptors for the herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) [164-166]. Increasing Nectin-1 expression resulted in increased susceptibility to HSV-1 infection and oncolytic activity and hence enhanced tumor regression *in vivo* [167]. Attenuated HSV-2 viral production in WB rat liver epithelial cells was found to depend on the viral protein co-localization with adherens junction proteins rather than by the status of gap junctions [168]. Taken together, these studies demonstrate the importance of junctional proteins in the infectivity of viruses and suggest that they might impact the efficacy of the viral oncolytic gene therapies. Compounds could thus be identified for example to improve viral gene transfer [169].

4.3. Intercellular communications-dependent protein-protein interactions

Many proteins, although not *bona fide* components of cell-cell junctions, are either affected by these interactions or are very important in the function of direct cell-cell interactions, whether junctional or not. Prototypes of these proteins are the ones involved in axon guidance, such as the Eph/Ephrin proteins. The Eph family is the largest family of receptor tyrosine kinases, and includes the A-type Eph (EphA1–10) and B-type Eph (EphB1–6) receptors as well as A-type Ephrin (EphrinA1-6) and B-type Ephrin (EphrinB1-3) ligands. A particularity of this family is that, with few exceptions, the receptor-ligand interactions depend on direct cell-cell contacts, as both Ephs and Ephrins are anchored in interacting cellular membranes and in fact their role in cell-cell repulsion/attraction and cell sorting is one of their main features. Study of Ephs/Ephrins' role in cancer has dramatically boomed in the last decade [170] and attempts are currently underway to target them in cancer therapy. Targeting of Ephs and Ephrins for gene therapy has been very timid so far. EphA2 is probably one of the most sought after receptors of this family, as its expression is increased in many cancers and it has shown pro-oncogenic functions. A human adenoviral type 5 (HAd) vector expressing a secreted fusion protein constituted of the extracellular domain of EphrinA1, an EphA2 ligand, fused to the Fc portion of IgG1, was used to infect mammary epithelial cells and was found to activate and induce the degradation of EphA2, thus showing anti-tumor effects. After intratumoral inoculation, the HAd-EphrinA1-Fc vector significantly inhibited tumor growth *in vivo* [171, 172]. On the other hand, taking advantage of the high expression levels of EphA2 in cancer cells, an EphA2-binding peptide has been added to an Adenoviral vector (Ad) to target pancreatic cancer cells and bypass the limitation of low Ad transduction due to low levels of the major Ad receptor called Coxsackie and Ad receptor (CAR) [173]. Recently, EphA2 has been shown to be an essential receptor for the Kaposi's sarcoma–associated herpesvirus, a major oncogenic virus in endothelial cells [174, 175]. EphrinB2 and EphrinB3, other family members, have also been identified as entry receptors for the Hendra virus and Nipah virus [176-178]. These data suggest that interfering with Ephs and Ephrins could be an interesting strategy in gene therapy applications by improving the transduction of viral vectors.

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5. Concluding remarks & perspectives

Over the years, it has become clear that various systems of cell-cell communication play critical roles not only in the normal development, architecture, remodeling and function of various tissues and organs, but in the onset of diseases as well. Cells are social entities and need to interact with each other in a way that ensures a favorable response to input from their immediate micro-environment (growth, survival, cytotoxicity) and a flexible adaptation to various roles and stress conditions. They also need to communicate during their death and demise. These communication processes are subject to various regulatory mechanisms which, when going awry, could result in various pathologies. One such instance where cell-cell communication has a particularly dramatic role is cancer progression, metastasis and response to therapeutic interventions. This reliance of cancer cells on cell-cell communication provides a therapeutic opportunity that will be fully exploited only if the mechanisms of its normal and aberrant functions are elucidated. This is for instance obvious when attempting to restore GJIC to render cancer cells sensitive to enzyme/prodrug therapies.

Also, cancer cells share their microenvironment with many other cell types who are not just neutral bystanders. In particular, invasive cancer cells have very unstable intercellular contacts, as they keep migrating, constantly adhering to and detaching from cells on their way and thus changing the nature of their cell-cell communications. This might be a challenging fact when thinking of gene therapy strategies, and in fact any other type of therapy. Thus understanding these dynamics of change during the course of tumor progression is of utmost importance.

As progress continues in developing strategies for a more efficient and selective viral delivery of gene therapeutics, the role of different junctions in the resistance of cancer epithelial cells to viral infections, needs to be balanced by the advantageous use of these proteins to render this approach more cancer-specific. In this respect, the enzyme/prodrug strategies need to be reconsidered in the light of the new findings that involve both gap junctions and other types of intercellular communications in the bystander effect. Examining the links between the different types of cell-cell communication will be critical for future applications.

Finally, the impact of protein-protein interactions which are not necessarily engaged in cell junctions but are involved in direct cell-cell interactions, and the therapeutic opportunities they provide, will constitute a way for the future.

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