Editorial

Gene therapy for lung cancer malignant pleural effusion: current and future nano-biotechnology

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Gene therapy has been applied to malignant pleural effusion derived from several types of cancer (colon, breast, lung cancer, mesothelioma, ovarian and liver) (1-5). Successful management has been established either with p53 tumor suppression gene therapy (4,5) or gene therapy as immunotherapy (1,3) and currently with pro-drug transformation (antibiotic) to active chemotherapy compound (2). All studies administered the nanocomplexe (viral vector/plasmid DNA) through a tunneled intrapleural catheter to induce local disease management. The nanoparticle used to deliver gene therapy in all previous presented studies was a viral vector. Viral vectors are known to stimulate the immune system and therefore formulate neutralizing antibodies (Nabs) against the nanocomplex (6). In addition, viral vectors exhibit higher gene transfection efficacy in comparison to non-viral vectors. However, they tend to induce flu-like symptoms upon administration; nevertheless, these symptoms are intermittent and well controlled with corticosteroid preparation and apamide at least 30 min before gene therapy instillation (3,4). In the study by Sterman *et al*. (3), it was investigated the time of initiation of the Nab formation, and it was proposed as a future direction that higher efficiency of this treatment modality would be achieved with a three day interval administration. Nevertheless, gene therapy with a viral vector is not proper for repeatable administration, there is no gene transfection observed after 14 days of administration (3). Therefore other groups pursued the addition of a chemotherapeutic agent for efficient local disease control, with success, but again the positive results observed were brief until Nabs where constructed (4,5). However, the concept of local tumor suppressor gene therapy and immunotherapy has the advantage of chemo- and radio- sensitization, boosting local disease control. The addition of a chemotherapeutic agent with gene therapy provides more effective local disease control; however, more trials are in need with gene therapy alone or with a chemotherapy agent. Cancer type plays a crucial role in the creation and maintenance of malignant pleural effusion (MPE). The behavior of MPE differs between the different cancer types. Although several components of the different cancer origin MPEs are the same, cancer cell population and pleura interaction differs. Local disease control is more appropriate for a malignancy affecting the pleura. Therefore gene therapy is more appropriate for mesothelioma cancer, since the pleura is affected. Although there are data regarding the diffusion of this therapy through the pleura porous to the blood circulation and lymphatic circulation, there are no data how this therapy affects a solid tumor within the lung parenchyma (7,8). More data are in need to present that gene therapy in MPE also affects a solid tumor, and it is not just another modality to induce pleurodesis.

Furthermore, the MPE environment is unfriendly for gene therapy due to chondroitin sulfates and proteoglycans/glycosaminoglycans, these molecules interact with the nanocomplex (Viral vector/plasmidDNA) and diminish the gene transfection (9). Experimentation to minimize the interaction was investigated with: (I) pre-treatment with corticosteroids (10); (II) alternate serotypes (11); (III) targeting the airway epithelium (12); (IV) pre- or co- administration of cytotoxic agent or immunotherapy

(13,14); and (IV) construction of viral vectors with both reduced immunogenicity and high DNA uptake (15). However, no definite solution was provided. Moreover, since the viral vectors are not an efficient drug delivery system for repeatable administration, due to Nab formation, additional investigation was pursued to overtake this drawback. The efforts were focused on the following: (I) modification of viral capsids (16); (II) polyetheleneglycol (PEG) coating to Ad vectors (17); (III) pretreatment with glucocorticoids (18); (IV) use of lipid bilayer coating (19); (V) masking of adenoviral fiber knob (20). Although the formation of Nabs was delayed the problem of the immune system activation against the vector/plasmid nanocomplexe still remained. Another approach was investigated by increasing the dosage of the Ad (plaque forming units), however, the adverse effects were also increased.

In order to create nanocomplex with the ability of repeatable administration the non-viral vectors where conjugated with plasmids (21). The polyethylenimine (PEI) has been investigated either as low molecular weight (2 kDa), or high molecular weight (25 kDa). It has been observed that low molecular weight <1.8 kDa does not present any gene transfection and high molecular weight >25 kDa present low cell viability (high toxicity). In addition, they are divided in liner and branched. Although an investigation is still ongoing regarding the safety profile of these vectors, results indicate higher efficiency for treatment repeatability in comparison to the viral vectors. The efficiency of the gene therapy nanocomplexe was further investigated by adding polyethyleneglycol coating to the non-viral vector PEI (22). Another nanocomplexe was created by Shi *et al*. (22) which has the ability to administer simultaneously a chemotherapy agent and gene therapy. This nanocomplexe is a breakthrough and has a possible application to many malignancies. It can sensitize and increase cancer cell apoptosis at the same time. Another, nanocomplexe that can be used as a delivery system for gene therapy is the pH-sensitive cationic lipid with PEG (23). The delivery of the gene therapy is initiated when the nanocomplexe comes in contact with a pH <6.5, this value is observed in cancer cells, when the pH in normal cells is >7.4. In addition, to exploring a more efficient nanocomplexe for local gene delivery, ligand coating to nanocomplexes was investigated (24). Non-viral vectors were added to the nanocomplexe of vector-plasmidDNA, such as: (I) vascular endothelial growth factor; (II) epidermal growth factor and recently; (III) fibroblast growth factor.

In conclusion, several approaches have been investigated to control MPE with gene therapy. MPE derived from lung cancer as a prime cancer site is not a good candidate for gene therapy, not only due to the major drawbacks from the vector/plasmid DNA nanocomplexe, but also due to the fact that the pleura in lung cancer (non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC)) are not actually the problem. MPE from mesothelioma should be further investigated, as these patients will actually benefit from the local gene therapy administration. Local control can be achieved by the tumor regression gene therapy (p53), gene immunotherapy, and nanocomplexe chemotherapy-gene therapy administration. In addition, enhancement of gene therapy can be achieved with the proper vector selection (non-viral) and nanocomplexe coating either with a ligand or PEG. Gene therapy is an expensive treatment modality and therefore it should be used in selected patients that will benefit. Patients with MPEs due to liver, ovarian, breast or even lung cancer, will not benefit from gene therapy as local disease control treatment, as for these patients this treatment modality will only present an efficient pleurodesis. Pleurodesis can be achieved with cheaper methods. In addition, data regarding the gene therapy penetration in solid tumors are in great need. There are data explaining the transport of nanocomplexes from the site of administration to the blood circulation and lymphatic circulation, however, there are no data indicating the concentration of the drug formulation that interacts with the tumor. All previously published studies presented data regarding the follow up of the patients, gene therapy transfection, and vector-plasmid-MPE interaction. Nevertheless, no data are presented regarding the nanocomplexe of vector-plasmid-solid tumor interaction. Another mode of gene therapy which merits to be further investigated in lung cancer (SCLC/NSCLC) and mesothelioma is the "bystander effect". We would like to have a pro-drug that efficiently penetrates solid tumors and is not toxic for normal cells. When the pro-drug is activated, only the cancer cells will be targeted and destroyed. This approach is very intriguing, since less systemic side effects will be observed, and less drug formulation concentrations are needed to observe disease control. Future efforts should be directed to gene therapy of MPE from mesothelioma prime cancer as local treatment modality, until further trials present data of solid tumor nanocomplexe interaction. Enhancement of the nanocomplexe targeted delivery to cancer cells can be

achieved by adding ligands as coating to the nanocomplexe shell. Finally, non-viral vectors should be further explored, but in the form of biodegradable cationic polymers (25). A degradable non-viral vector has the ability to be constructed in large molecular weights nanocomplexes and uptake more DNA material, where at the same time will degrade fast enough to prevent *polyethylenimine* (PEI) induced toxicity. A comparison through different solid tumors is also welcomed to observe the different interactions with the nanocomplexes and gene therapy modalities.

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