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Editorial

Immunoliposomes-mediated small interfering RNA therapy: A novel approach for the treatment of cancer

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The occurrence of cancer has been expanding steadily with the aging and growth of the world population altogether. According to the data published by GLOBOCAN 2018, an approximately >18 million new cases of cancer prevalence as well as 9.6 million cancer-related mortality are estimated to be reported in 2018.[1] Despite advances made in its treatment, deaths from cancer are continuously rising with an estimated 17 million deaths in 2030.[2]

As we know that the dysregulation of molecular signaling pathway due to changes in either proto-oncogenes or tumor suppressor gene lead to cancer initiation, promotion and progression as well. Irrespective of vast expansion of knowledge concerning the mechanisms and molecular lesions in the growth of human neoplasia in approximately four decades, only a few of these findings have led to changes in the diagnosis and treatment of cancer.[3]

The existing methodologies for the treatment and surgical interference are not enough to deal with this dreaded disease, and therefore, the continuous efforts are ongoing to explore the novel targets and strategies for the management of carcinogenesis.

As evident from several studies, the activated proto-oncogenes are preferential therapeutic targets in comparison to tumor suppressor genes, as the upregulation of proto-oncogenes can be restored to the reduced activity in tumor cells.[4]

Transcription factors have recently been appearing into focus as drug targets as their downstream targets contain the majority of oncogene products.[5] Hence, these transcription factors may provide the advantage of targeting one gene or its product instead of numerous different signaling molecules. This may reduce the chances of chemotherapy resistant through upregulation of alike signaling mechanism.

The finding of RNA interference approach has made revolutionary development in molecular biology by allowing discerning knockdown of genes more effectively in comparison to previously established technology.[6] The double-stranded RNA molecules with the length of 19–23 base pairs are used as a small interfering RNA (siRNA) offers a widely applicable tool for not only research-based investigations but also potential therapeutic interventions. Such siRNAs are either produced by Dicer or administered exogenously, making a RNA-induced silencing complex. This complex is guided to the homologous location on the target mRNA to promote its specific cleavage and incorporates antisense strand of unwound siRNA through complementarity in the sequence.

However, irrespective of recent developments in siRNA research, the in vivo delivery to its intended cell type, tissue, or organ is the most challenging obstacle faced by siRNA therapies. Thus, an active uptake mechanism is required for effective siRNA therapeutics. The targeted delivery of siRNAs has been shown a promising tool in gene silencing. However, it also has the same challenges and hurdles of site-specific delivery of other small molecule drug therapeutics, which includes serum stability, target tissue accumulation and penetration, pharmacokinetics, and bio-distribution. Remarkably, the most of the small molecule drugs diffuse passively in the surrounding cells, but siRNA is required to be delivered to the appropriate subcellular localization, i.e., the cytosol following internalization to attain a potential gene silencing effect.[7]

Immunoliposomes have become feasible, novel strategy as a result of parallel advances in the areas of liposome research and map technology, which in principle can be applied for targeted delivery in cancer. Evidently, sterically stabilized PEGylated long-circulating, small, neutrally charged liposomes have led to a new era in liposome-based drug delivery system. It showed retarded clearance by reticuloendothelial system (RES), which subsequently leads to prolonged drug circulation. Moreover, the small sizes and prolonged circulation of these liposomes led to enhanced extravasation in various solid tumors as the

vascular abnormalities associated with tumor angiogenesis. Nevertheless, the sterically stabilized liposomes release drug for eventual diffusion into the cancer cells but do not participate in the direct interaction with the cancer cells *in vitro* or *in vivo*.[8]

The development of a site-specific immunoliposomes delivering siRNA represents a practical way in cancer gene therapy. The tumor therapy involving antibodies or antibody-derived molecules coupled liposomes encapsulating siRNA has been considered one of the most promising approaches to reach to the tumor cells directly through surface antigen binding and uptake into the targeted cells.

As described above that, immunoliposome in which the antibodies are engrafted at the distal end of polyethylene glycol (PEG) chain is an advanced form of long-circulating immunoliposomes. It has been shown more advanced site-specific delivery vehicle in comparison to conventional immunoliposomes without PEGylation. These sterically stabilized long-circulating immunoliposomes decrease the interactions with plasma proteins due to the free PEG chains which are not linked to antibodies. As a result, it avoids the uptake of liposomes by RES ensuing elevated blood concentration and enhanced targeting of such formulations. It is evident that intact antibodies attached to the surface of liposomes are likely to be immunogenic and promptly removed by Fc-mediated phagocytosis by macrophages. Such hindrances can be evaded using Fab or scFv molecules as ligands which can be easily customized accordingly through cloning of constructs, which make a very defined and site-specific linking to the reactive group of liposomes.

Interestingly, most of the drug molecules entrapped in the immunoliposomes are degraded as lysosomes are the crucial destination following the internalization after receptor-mediated endocytosis. Therefore, pH-mediated drug release approach can be established using pH-sensitive liposomes (PSLs) to overwhelm this problem.[9] PSLs release their contents after destabilization and attain the fusogenic properties at mildly acidic pH. Thus, the entrapped contents in the PSLs are released in the cytoplasm following entry inside the cell through the process of endocytosis due to the acidic pH of the endosomes. Furthermore, the concept of PSLs is exceptionally suggested to apply for some pathological tissues, which show an acidic environment. Liposomes comprising 1,2-Dioleoyl-sn-glycero-3-phosphatidylethanolamine (DOPE) and cholesteryl-hemisuccinate (CHEMS) are the most recognized PSLs due to the presence of DOPE, which is a crucial factor determining the ability of PSLs to undergo the destabilization on acidification. The delivery of liposome-entrapped contents is occurred after achieving the hexagonal inverted phase by the lipids in acidic environment. In addition, CHEMS is also the essential component to provide sufficient stability to PSLs.

It is believed to explore the advantage of each of these properties while combining selectively all, resulting in an increased or synergistic therapeutic efficacy. The site-directed targeted delivery for most of the cells and tissues has yet to be optimized distinctly. The strategies will probably need to be customized for each target cell type and the markers of the disease.

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