Chapter-15

Biomimetics in Oral Cancer and Diabetes Research

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Abstract

Biomimetic is an upcoming field wherein naturally derived or artificially synthesized substances are used for treating various disease conditions by utilizing nanoparticle based therapeutic materials. These have distinct advantages over conventional therapeutic medications due to ease of penetrability, rapid onset of action and long duration of action. There are novel advancements in use of nanomedicinal technology using biomimetic substances in treatment of diabetes and oral cancer. This review paper deals with biomimetic ongoing research in treatment of diabetes and oral cancers.

Keywords: Biomimetics, Nanomedicines, Nanoparticles, Diabetes, Oral Cancer

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1. PANCREATIC PATHOPHYSIOLOGY IN DIABETES MELLITUS

Endocrinal progenitor cell population within pancreas exhibit expression of transcription factor '*Pdx-1'*along with pro-endocrine transcriptional factor, Ngn3 [1, 2,3]. Pro-α-cells show expression of pro-glucagon gene as well as pro-hormone convertase enzyme '*PC1/3'* during initial endocrine cell lineage during early embryological development. *PC1/3* leads to production of GLP-1 that functions primarily as growth factor in proliferation as well as differentiation of pro-α-cell populations.[4] Ratio between expressions of *Arx:Pax4* transcriptional factors has a direct relation between differentiation into α- and β- pancreatic cells. Mature 'α'-cells show expression of '*PC2'*, leading to glucagon production. [4]

α pancreatic islet cells have a protective role over pancreatic β-cells besides a supportive role in paracrine functional mechanisms. Quantity of α pancreatic islet cells have been shown to increase in response towards stress and impairment of β-cells. [5]

Diabetic Pathophysiology and Biomimetic Medicines

Individual suffering from type II diabetes develop complications of micro- as well as macrovascular system such as- nephropathies, retinopathies, neuropathies, cardio-vascular disorders along with cerebral stroke. Conventional anti-diabetic therapy has side-effects such as- gain of weight, hypoglycaemic state and side-effects of gastro-intestinal system. [6] glucagon-like peptide 1 receptor agonist or GLP-RA1 is an incretin hormone that undergoes secretion from intestinal L cells as a response towards high levels of glucose by stimulation of insulin and by suppression of secretion of glucagon in glucose-dependent manner. [7] GLP-1 also acts as a neurotransmitter substance which is synthesized in the pre-proglucagon neurons within brain. It functions via central brain pathways in order to lower intake of ATP by affecting hunger, reward-associated functions and satiety. Drugs based on GLP-1 have benefit of once or twice weekly consumption. Examples of GLP-1 against drugs are- Liraglutide and Semaglutide. Both of these drugs have a single fatty acid as well as modification of linker. Both Liraglutide and Semaglutide are excellent carriers meant for sustained PNP hydrogel depot delivery. Polymer-NP hydrogel formulations provide application-based biomolecular release of proteins or vaccines. [8, 9]

Biomimetic Therapy against Tumors

Nanoparticles alter pharmacokinetics of drugs. Biomimetic materials that are cell-derived / based can be used as nanocarriers for active tumor targeting.

These functional substances act by activation of immunological system for anti-tumorous activity. Liposomes constitute bilayer cell structures that is identical to biological membranes. These are artificially synthesized bionic membranous structures and have excellent biological compatibility and capacity for loading drugs and may contain hydrophilic as well as hydrophobic drugs. The liposomal cell surface is modifiable for improvement of activities that are drug targeting. Liposomes are currently widely used as nanocarriers of anti-cancer drugs. These have synthetic membranous structures comprising of phospholipids with cholesterol. Phospholipids form bilayered structures with closed vesicle based structure as a result of their amphophilic nature. Cholesterol helps in stabilization of liposomal structure. [10]

Classification of Biomimetic Nanomedicines

Biomimetic nanomedicinal products can be classified into two types:

1. Biological Derivatives
2. Artificial Derivatives.

Biological Derivatives are of Following Types:

1. Macrophage Derived
2. B-Lymphocytic Derived
3. Red Blood Cell Derived
4. Stem Cell Derived
5. Cancer Cell Derived

Artificially Derived Biomimetic Nanomedicines are of Following Types:

1. Vesicle Derived
2. Protein Derived
3. Micelles
4. Nanospheres
5. Nanoparticles

Nanoparticle Based Treatment of Diabetes

Insulin release vesicles that are based upon different conformational as well as morphological alterations caused by ‘glucose oxidase’ metabolism. It has rapid activity, excellent biocompatible properties and has ease of administration. As there is a risk in extra-cellular levels of glucose, fusion of insulin occurs with cell membrane that results in an increase in secretion. This has a bilayered structure due to copolymeric polyethylene glycol-poly-O-acetryl serine nanoassembly. The enzyme ‘Glucose oxidase’ causes catalysis of glucose conversion to glucuronic acid that causes reduction in local pH along with triggering of hydrolysis of ketone acids. [11]

Lipids modified using dopamine after addition to liposomes form bonds between catechol and phenyl-boronic acid group and binding with Fc receptors. These molecular imprinted polymers are available as nanosized materials with have biomimetic polymeric nanosensors.

Nanoparticles' Based Treatment of Cancer: Use of inorganic nanoparticles like silica, silver and organic nanoparticles like- polymers along with cellular membranes allows targeting of cancer cells. [12]

Liposomal Membrane Based Modifications in Different Cells for Nanoparticle Delivery

1. **Red Blood Cells:** The cell membrane covering of red blood cells have been structurally modified to enable better delivery of drugs to tumor cells. CD44, a tumor ligand has been targeted for binding by these altered red blood cells by hyaluronic acid which is a CD44 ligand.

2. **Platelets:** Platelets contain multiple cell surface receptors which allows then to communicate with tumor micro-environment. These cells extend nanocarrier circulation by evasion of immunological detection. P-selectin on platelet surface undergoes binding with CD44 receptors on tumor cells. Platelet membranes that have been encapsulated with lysosomes demonstrate an increase in their ability for evading immunological clearance by CD47 membrane expression.

3. **Dendritic Cells:** Immunotherapeutic medications based upon dendritic cells can be utilized for delivery of 'peptide'-based antigens by enabling memory T-helper lymphocytes. Dendritic cell derived membranous vesicles can amplify T lymphocytes. Incorporation of nanoparticles within dendritic cell membranes leads to their localization within lymph nodes, thereby, causing activation of acquired immunological responses.

4. **T-Cell Derived Biomimetic Molecules:** T cell receptors specifically act against gp100. Nanoparticles encapsulated within T cell membrane act as carriers of drugs against tumors. These nanocarrier molecules act upon heterogenous tumor cell population and destroy them.

5. **NK Cell Based Biomimetic Substances:** NK cells specifically target tumor cells specially once that have features of stem cells. Liposomes fused with NK cells or NKsomes have non-immunogenicity. These NKsomes target tumor cells by acting upon their cell membranes. NK cell membranes' proteins cause promotion of M1 type macrophage polarization and facilitation of tumor cell activity. NK-cell based membranous vesicles act by suppressing tumor immunological micro-environment resulting in building

up of anti-tumor immunity. Biomimetic molecules functionally convert the tumor associated macrophages to M1 cell type leading to conversion of 'cold' to 'hot' tumors. NK cell-based biomimetic substances target the tumor cells by allowing aggregation, activation as well as improve cell proliferation within tumors. [13]

6. **Lipid-Hybrid Based Tumor Cells Derived Biomimetic Substances:** These functional bomimetic materials are prepared by membranous embedding of glioma cell membranes within liposomes that enables them in crossing blood brain barrier. The tumor derived membranes enhance active targeting by nanoparticls due to homotypic type of binding between nanoparticles and tumor cells.[13] Nanoparticle that are laden with drugs using cell membrane encapsulation can be used as anti-tumor vaccines that can activate the anti-tumor immunological system. [13]

7. **Lipid-Based Bacteria Derived Biomimetic Materials:** Bacteria can be used as therapeutic modalities either singly or in combination with anti-cancer treatments to reduce recurrence as well as metastases. Examples of these bacterial populations include- E. coli and S. typhii. High intensity focused ultrasound has been found to cause ablation of tumor tissues and controlled drug release or treating benign as well as malignant conditions. However, treatment of deeply seated tumors is difficult to achieve due to decreased propagation of ultrasound waves. [14, 15, 16]

However, bacteriotherapy derived treatment protocols have not shown regression of tumors and are also capable of inducing serious side-effects in high dosages.[16]

Applications of Lipid-Derived Biomimetics/Biosimilars

1. **Chemotherapy:** Chemotherapy, a widely used treatment modality in cancers can cause chemoresistance. Various nanocarrier formulations have been designed that can infiltrate tumor-associated vasculature. However, the biggest drawback is inefficient delivery of drugs due to high fluidic presence in tumors owing to increased endothelial spaces and also, due to excessive production of extracellular matrix. [17]

2. **Radiotherapy:** In this type of treatment, ionizing radiation is employed through focused and highly energized ϒ- or X-rays on cancerous cells for inducing damage to DNA and production of reactive oxygen species. However, elevated GSH (Glutathione) levels in tumor tissues act as hindrance towards radiotherapy. Hence, in order to make radiotherapy effective GSH should be converted to its oxidized form for depleting it in

tumor microenvironment by means of MoS_2 nano-carriers or use of palmitoyl ascorbate micelles. [17, 18]

3. **Phototherapy:** Main drawback associated with surgical treatment is that there is incomplete removal of tumor cells whereas chemo- and radiation therapy are associated with side-effects. However, phototherapy involves conversion of light energy to chemical/thermal energies by generation of photosensitizers that kill tumor cells by absorption of light which is converted to heat energy. This increases temperature at targeted site, thereby killing the cancerous cells. Development of various nanocarriers for delivering photosensitisers via biomimetic materials is an ongoing research area. [19]

4. **Immunotherapy:** Tumor vaccines utilize tumor associated antigens for triggering immunological response against tumor cells. [10, 21]

Biomimetic Nanomedicines in Treatment of Various Diseases [22]

Various biomimetic nanomedicinal products that are used for treatment of diseases include:

1. **Natural Membrane Derived:** Tumor cell membranes specifically target tumor cells and possess cellular internalizing properties.
2. **Red Blood Cell Membranes:** RBC membranes improve circulation of drug, superior penetrability of blood brain barrier, accumulation within tumor masses as well as retention.
3. **Platelet Membranes:** These enhance circulation in blood and targeting of tumors.
4. **Derivation from Bacterial Cell Membranes:** These enhance the tumor microenvironment by promoting immunosuppression.
5. **Chimeric T Lymphocytic Antigen Receptor Membranes:** These have shown high specificity in hepatocellular carcinoma photothermal treatment.
6. **Macrophage Derived Membranes:** These are helpful in targeting drug delivery within inflammatory colonic tissues.
7. Human serum albumin derived membranes promote high accumulation along with long retention time.

Hybrid membranes manufactured by combination of macrophages with tumor membranes:

- **Stem Cell Membranes:** These form nanocomplexes that mimic exosomes that aid in escaping the immunosurveillance system.

Artificial Biomimetic Nanomedicinal Agents

- Higher density lipoproteinaceos core shell nano-platforms (in atherosclerotic patients).
- Poly LGA (Lactic co-glycolic acid): Nanoparticles contain cationic octa-arginine peptide along with anionic phosphor-serine. This has fast penetration within mucin and can aid in oral delivery of insulin.
- Biomimetic insulin imprinted polymeric nanoparticles for oral insulin delivery.
- Cerium laden Linde type a zeolite-derived nanomaterial (in ischaemic diasease).
- Biomimetic-based liposome (in myocardial infarction).

Advantages of Biomimetic Nanomedicinal agents

1. Lower immunological responsiveness and higher biological compatibility.
2. Since these cannot be easily recognized byb host immunity system, they have higher duration of circulation.
3. Nanoparticle based agents show much enhanced tumor targeting due to enrichment at targeted sites. [23]

Bio-Fabrication and Bio-Printing in Diabetes

Bio-fabrication can be defined as "an automated generation of biological functioning products that have a structural organizations similar to living tissues, bio-active molecules, bio-materials, cell-based aggregates like- micro-tissues, hybrid constructs between cells and material via bio-printing and/or bio-assembly."[24]

Bio-printing technology involves advanced technology in tissue engineering which involves layer-by-layered arrangement constituted by wide arrays of cells, bio-materials as well as biologically active factors in a precise manner. [25] This new emergent technology is promising in the field of regenerative medicine for simulating native tisse-related environment for fabricating clinical tissues along side *in vitro* 3D study models for screening of therapeutic effects. [26] A bioprinting cartridge contains different cell combinations within hydrogel based biomaterials as basic scaffolds or bioinks. [27]

3-dimensional bio-printing can fabricate as well as raise the levels of islets along with supportive cells as well as biologically active factors for survival of transplanted islet cells. [28] This extrusion-based bio-printing method can be used for fabricating functional tissue akin to pancreatic islets.

Use of artificial intelligence technique can also help in designing tools for cancer diagnosis and treatment with management.

2. CONCLUSION

Use of novel nanomedicines, nanoparticles, bioprinting, biofabrication amongst other technologies for treatment of diabetes and cancer is the current trend in disease management. Future approach in this field must be towards making these technologies more patients friendly.

REFERENCES

[1] Kassem SA, Ariel I, Thornton PS. Beta-cell proliferation and apoptosis in the developing normal human pancreas and in hyperinsulinism of infancy. Diabetes 2000;49:1325–33.
[2] Gradwohl G, Dierich A, LeMeur M. Neurogenin3 is required for the development of the four endocrine cell lineages of the pancreas. Proc Natl Acad Sci U S A 2000; 97:1607–11.
[3] Johansson KA, Dursun U, Jordan N. Temporal control of neurogenin3 activity in pancreas progenitors reveals competence windows for the generation of different endocrine cell types. Dev Cell2007;12:457–65.
[4] Habener JF, Stanojevic V. α-cell role in β-cell generation and regeneration. Islets 2012; 4:188–98.
[5] Willcox A, Richardson SJ, Bone AJ. Evidence of increased islet cell proliferation in patients with recent-onset type 1 diabetes. *Diabetologia* 2010;53:2020–8.
[6] Aquino AI, Maikawa CL, Ngujen LT, Andersen HB, Simonsen L, Appel EA. Use of a biomimetic hydrogel depot technology for sustained delivery of GLP-1 receptor agonists reduces burden of diabetes management. Cell Reports Med 2023;4:101292-301.
[7] Ranganath LR. Incretins: pathophysiological and therapeutic implications of glucose-1 dependent insulinotropic polypeptide and glucagon-like peptide-1. J Clin Pathol 2008;61:401-9.
[8] Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes state-of-the-art. Mol Metab 2021;46:101102-4.
[9] Appel EA, Tibbitt MW, Webber MJ, Mattix BA, Veiseh O, Langer R. Self-assembled hydrogels utilizing polymer-nanoparticle interactions. Nat Commun 2015;6:6295-300.
[10] Liu WS, Wu LL, Chen CM, Zheng H, Gao J, Lu ZM et al. Lipid-hybrid cell-derived biomimatic functional materials: A state-of-the-art multifunctional weapons against tumors. Materials Today Biol 2023;22:100751-5.
[11] Palanikumar L, Kim HY, Oh JY. Noncovalent surface locking of mesoporous silica nanoparticles for exceptionally high hydrophobic drug loading and enhanced colloidal stability. Biomacromolecules 2015;16(9):2701-4.
[12] Benyettori F, Rezgui R, ravaux F. Synthesis of silver nanoparticles for the dual dlivery of doxorubicin and alendronate to cancer cells. J Mater Chem B 2015;3(36):7237-45.
[13] Liu L, Pan D, Chen S, Martibarner MV, Karlund A, KE J et al. Systematic design of cell membrane coating to improve tumor targeting of nanoparticles. Nat Commun 2022;13(1):6181-6.
[14] Zhang L, J Yi, J Song, K Huang, B Yang, D Tan et al. Mitochondria targeted and ultrasound- activated nanodroplets for enhanced deep penetration sonodynamic cancer therapy. ACS Appl Mater Interfaes 2019;11(9):9355-66.

[15] Go Y, Chen Y, Liu X, Min JJ, Tan W, Zheng JH. Targeted cancer immunotherapy with genetically engineered oncolytic Salmonella typhimurium. Cancer Lett 2020;469:102-110.
[16] Mai X, Chang Y, Yon Y, He L, Chen T. Designing intelligent nano-biomaterials with on-demand site-specific drug burst release to synergise with high-intensity focused ultrasound cancer ablation. J Contr Release: Official Jornal of the Controlled Release Society 2021;331:270-81.
[17] He B, Sui X, Yu B, Wang S, Shen Y, Cong H. recent advances in drug delivery systems for enhancing drug penetration into tumors. Drg Deliv 2020;27(1):1474-90.
[18] Wang KX, Ciu WW, Yang X, Tao AB, Lan T, Li TS et al. Mesenchymal stem cells for mitigating radiotherapy side effects. Cells 2021;10(2):343-6.
[19] Lyu M, Zhu D, Kong X, Yang Y, Ding S et al. Glutathione-depleting nanoenzyme and glucose oxidase combination for hypoxia modulation and radiotherapy enhancement. Advanced healthcare Materials 2020;9(11):e1901819-21.
[20] Yang Y. Cancer immunotherapy: harnessing the immune system to battle cancer. J Clin Invest 2015;125(9):335-7.
[21] Liu WS, Wu LL, Chen CM, Zheng H, Gao J, Lu ZM et al. Lipid-hybrid cell-derived biomimetic functional materials: A state-of-the-art multifunctional weapon against tumors. AMterials Today Bio 2023;22:100751-75.
[22] Serio F, da Cruza F, Chandia A. Electrospun polyvinyl-alcohol/gum Arabic nanofibers: Biomimetic platform for in vitro cell rowth and carrier nanomedicine delivery. Int J Biol Macromol 2021;185:764-7.
[23] How H, Chen Y, Wu M. Biomimetic nanomedicine towards personalized disease theranostics. NAno Res 2020;14(8):2494-2511.
[24] Moroni L, Boland T, Burdick JA. Biofabrication: A guide to technology and terminology. Trends Biotechnol 2018;36: 384–402.
[25] Ng WL, Chua CK, Shen Y-F. Print me an organ! Why we are not there yet. Prog Polym Sci 2019; 97: 101145.
[26] He J, Mao M, Li X. Bioprinting of 3D functional tissue constructs. Int J Bioprint 2021; 7:395-41.
[27] Mironov V, Trusk T, Kasyanov V. Biofabrication: A 21st century manufacturing paradigm. Biofabrication 2009; 1: 022001-3.
[28] Liu X, Carter SD, Renes MJ. Pancreatic islet transplantation: Development of a coaxial 3D printing platform for biofabrication of implantable islet-containing constructs. Adv Healthc Mater 2019; 8: 1970029-31.