Medical Materials & Clinical Technology
Nano-particles based novel schemes for super-resolved imaging, medical diagnosis & treatment

Zeev Zalevsky, Tali Ilovitsh, Asaf Ilovitsh, Omer Wagner, Dror Malka, Adi Vegerhof, Yossif Danan, Rachela Popovtzer and Moshe Sinvani

Faculty of Engineering and the Nanotechnology Center, Bar Ilan University, Ramat-Gan, 52900, Israel

Abstract

In this paper we will present the overview of our research in which usage of special nano particles either made out of gold or from ferromagnetic material, either being spheres or rods, can be used to large variety of applications including super resolved imaging, detection of cancer borders in malignant tissue, as well as for bio-treatment. In the first part of the presentation we use ferromagnetic nano particles coated with amine shell. Those nano particles are targeted towards a malignant tissue and adapted to the near infra-red spectral region in which tissues are more transparent generate small heating of the cancerous tissue which allows improved detection of the borders of the cancer when inspected with thermal camera [2]. In the third part of the presentation we discuss novel schemes for realization of a nanoscope. The super resolved imaging concept is based upon the random (Brownian) movement of nano metric gold nano particles inserted into the inspected sample and used to apply localization algorithms and thereafter to construct a super resolved image with resolution matching the localization algorithms performance [3-5]. Since the localization precision is much higher than two points separation capability (the regular imaging resolution) of the microscope, the result is a label free nanoscope capable of imaging of nano metric intracellular features.

Keywords: Super resolved imaging; gold nano particles, Cancer boarders detection, thermal imaging, photo thermal therapy

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Figure 1 presents the usage of various types of nano-particles for sensing and bio-treatment: (a)-(d). Schemes of different configurations to be presented and discussed. (e)-(g). Some experimental examples of the obtained results.

Fig. 1. (a). (b). Usage of ferromagnetic nano-particles that are manipulated by external alternating magnetic field in order to image and to destroy more efficiently cancerous cells. (a). Scheme of 50nm ferromagnetic core coated with an amine shell. (b). Schematic design of the experimental setup. (c). Usage of gold nano-rods to performing efficient detection of borders of cancerous tissue by using thermal imager. (d). Usage of gold nano-particles for realization of localization based nanoscope to perform imaging of intra-cellular structures. (e). Cell viability test. 74x4 A431 cells in Petri dishes. Left untreated cells, middle treated cells. Right: treating head and neck cancer in mouse. (f). Thermal images of sample including a border between region with and without gold nano rods (GNR). Left is without irradiation and right is after 10 seconds of continuous illumination. (g). Examples of super resolution obtained with freely moving gold nano spheres. Left is the low resolution image, on its right is the super resolved one. In the right part of the figure we present the 3D reconstruction of a single A431 cell.
Diverse Role of Smads in Cardiac Remodeling: Mechanisms and therapeutic implications

Hui Yao Lan

Department of Medicine and Therapeutics, Li Ka Shing Institute of Health Sciences, CUHK-Shenzhen Research Institute, The Chinese University of Hong Kong, China

It is now well accepted that TGF-beta/Smad signaling is a major pathway leading to cardiac fibrosis. Among this pathway, we found Smad3 is pathogenic, while Smad7 is protective because deletion of Smad3 protects against but disrupted Smad7 enhances hypertensive cardiac remodeling and functional injury in a mouse model of hypertension induced by subcutaneous angiotensin II (Ang II) infusion. We also examined the mechanism by which Smad3 mediates cardiac fibrosis by RNA-seq and found that deletion of Smad3 prevents a loss of miR-29 family, suggesting that the miR-29 family is the downstream target of Smad3 and Smad3 mediates cardiac fibrosis by downregulating miR-29 expression. We then develop novel therapeutic strategies by targeting Smad3 signaling with a Smad3 inhibitor or by overexpressing Smad7, or by restoring miR-29b. All therapeutic strategies demonstrate that blockade of Smad3 directly with a Smad3 inhibitor or by overexpressing Smad7 is capable of inhibiting cardiac inflammation and fibrosis in the hypertensive heart disease. In addition, we also find that overexpression of miR-29b is able to blocking angiotensin II-induced cardiac fibrosis by inhibiting TGF-beta/Smad3 signaling, suggesting a feedback loop of TGF-beta/Smad3-miR-29 in Ang II-induced cardiac fibrosis. In summary, TGF-beta/Smads diversely regulate cardiac remodeling. Smad3 is a key mediator leading to cardiac fibrosis while Smad7 is protective. Targeting Smads by a Smad3 inhibitor, Smad7 agonist, or miR-29 may represent a novel and specific therapy for cardiac fibrosis.

Keywords: cardiac remodeling; Smad3; Smad7; microRNAs

Acknowledgements
This work is supported by Lui Che Woo Institute of Innovative Medicine - CARE Research Fund (8303307).
Receptor mediated endocytosis of multifunctional polylactitol-based gene transporter with siOPA1 for liver cancer therapy

Rohidas B. Arote*, Minhye AHN

Department of Molecular Genetics, School of Dentistry, Seoul National University, Seoul, 08826, Korea

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Schematic illustration of PLT-siRNA endocytosis

Abstract

The recent inventions to treat liver cancer have been undergoing significant shift in the “target-specific and long term control therapeutics”. The need for safe and efficient methods for gene delivery still remains a critical obstacle to the routine clinical implementation of human gene therapy. Viral vectors are currently the most efficient gene transfer agents. However, major concerns like immunogenicity, difficulty in large scale production have resulted in parallel efforts to develop non viral alternatives. Polyethylenimine (PEI) is a non- degradable gene carrier with high transfection efficiency. Also, the PEI has high cytotoxicity, which is dependent on its molecular weight. Gene therapy using non-viral vector for treatment of liver cancer can satisfy above-mentioned key points; not only useful to achieve long-term therapeutic efficacy by transferring therapeutic genes in liver cells, but also efficiently target cell-surface receptors such as asialoglycoprotein receptor (ASGPR) and Glucose transporter2 (GLUT2) receptor, which are over-expressed on the liver. Here, we engineered a new multifunctional polymeric Nano carrier, polylactitol-based gene transporter (PLT) to transfer therapeutic siRNA into liver, by crosslinking low molecular weight polyethyleneimine (B-PEI) with lactitol diacrylate (LDA). PLT was synthesized by reacting LDA and BPEI by Michael addition reaction. The complexation of polymer/siRNA was characterized by gel retardation assay, dynamic light scattering (DLS) and transmission electron microscopy (TEM) to determine the complex forming ability, particle size and morphology, respectively. The copolymers were analysed for their cytotoxicity and transfection efficiency on cultured HeLa, human cervical epithelial carcinoma cell lines, HepG2, human hepatoblastoma cell lines and A549 cells (Lung adenocarcinoma epithelial cells, human). In vitro cytotoxicity of PLT/siRNA and PEI25K/siRNA were evaluated by MTS assay and the silencing efficacy was evaluated using luciferase siRNA (siLuc) assay. The nano-complexes revealed lower cell cytotoxicity than that of PEI in all three different cell lines at wide N/P ratios. Polyplexes also revealed significant silencing efficiency in a dose dependent manner in three different cell lines. Our data revealed an emergence of novel multifunctional nano-carrier to treat liver cancer and open up a new strategy for siRNA delivery by using three different properties of PLT: 1) hyperosmotic part triggers caveolae-mediated
endocytosis, 2) galactose part can deliver genes into the hepatocyte via receptor-mediated endocytosis, and 3) PEI part assists rapid endosomal escape of gene due to proton sponge effect.

**Keywords:** Polylactitol-based gene transporter; siRNA; Liver cancer.

**Acknowledgements**

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korea Government (MSIP) (2015-R1A2A2A03004448) and the Oromaxillofacial Dysfunction Research Center for the Elderly (No. 2015-048003) at Seoul National University, Korea.

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Functional nutrition to modulate oxidative stress in Type 2 Diabetes and its complications in South Africa

George G1, Mutanhuki MR2, Ganjifrockwala FA3 and Joseph JT4

1-4 Division of Medical Biochemistry, Department of Human Biology, Faculty of Health Sciences, Walter Sisulu University, PMB X1, 5177, Mthatha, South Africa

Abstract:

World Health Organization has projected Non Communicable diseases (NCDs) as the biggest cause of death in the African region by the year 2030. In a recent analysis on the burden of disease in the country, South African Medical Research Council (SAMRC) has reported 39% mortality due to NCDs1. Type 2 Diabetes is one of the major NCDs in both urban and rural communities in South Africa2. Oxidative stress has been implicated in the genesis and progression of this chronic condition and its consequences such as micro and macro-vascular diseases3. The present study set out to evaluate the oxidative stress and antioxidant status of diabetic patients in a rural community in the Eastern Cape Province of South Africa and its relationship with biomarkers of diabetic control. The study also aims to identify lesser known underutilized dietary components in the rural diet which may have the potential to alleviate oxidative stress in resource poor settings. 40 diabetic patients (5-10yrs duration), no known secondary complications and are receiving treatment in a rural clinic and 20 apparently healthy controls (age matched) from the same community were recruited in to the study after informed consent. Anthropometric measurements, Selected biomarkers for diabetic control (Glycosylated Haemoglobin(HBA1c), Triglyceride (TG), Total Cholesterol(TC), HDLc, LDLc and Oxidized LDL) and oxidative stress parameters (malonaldehyde (MDA), thiobarbituric acid reactive substances (TBARs), Total antioxidant Capacity (TAO) were analysed using standard laboratory procedures. Clinical characteristics of the diabetic patients were compared with apparently normal controls. Statistically significant increases were found only in fasting blood glucose (p=0.0001) and HBA1c (p=0.0001). Comparison between controlled diabetics (HBA1c 6.15±0.59) and uncontrolled diabetics (HBA1c 9.23±1.87) were statistically significant at p<0.0001. No significant differences were observed between controlled and uncontrolled diabetics in lipid profile (TG, TC, LDLc and HDLc) but oxidized LDL was significantly increased (p<0.001) in uncontrolled diabetics. Similar increases were observed in the other oxidative stress parameters MDA (p<0.002), TAC (p<0.0002). The activity of the super oxide dismutase (SOD) enzyme was significantly reduced in uncontrolled diabetics (p< 0.0001). The trends observed in the rural diabetic population is of great concern as increased oxidative stress is implicated in the development of micro and macro-vascular complications. The importance of the total antioxidant capacities of the serum together with oxidative stress parameters is emphasized in order to assist timely intervention to avoid and delay morbidity and mortality. Lifestyle changes, affordable cost effective functional nutrients (available in resource poor setting) are recommended in this community to reduce the burden of diabetes. The presentation also will also focus on some of the lesser known underutilized indigenous leafy vegetables and their possible role in the reduction of NCD burden in the community.

Key words: Non communicable diseases, Disease burden, Type 2 Diabetes, Oxidative stress, Antioxidants,
Acknowledgement:

South African Medical Research Council & Walter Sisulu University are gratefully acknowledged for financial support.

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   http://dx.doi.org/10.1155/2016/2063103
Effect of various physico-chemical parameters on Rheological behavior of Sodium Alginate

Doha Berraouan¹, Abdesselam Tahani¹

¹Laboratory of physical chemistry of natural resources and Environment, Oujda, 60000, Morocco
*Corresponding author. Tel: (+212) 611202689; E-mail: dohaberraouan@gmail.com

ABSTRACT

Sodium alginates are widely used as gelling agent, coagulant, thickener and encapsulant in several industries. Since they can be used in aqueous solutions, it becomes more interesting to study their rheological behavior as non-Newtonian fluids and how adding divalent cations such as Calcium can influence it. In this work, intrinsic viscosity and rheological behavior of sodium alginate in different salt concentrations have been investigated. Obtained data have shown that the salt concentration plays a key role in the crosslinking process of this polymer.

Keywords: Sodium Alginate, Ca²⁺ binding, Rheological properties; Intrinsic viscosity

Acknowledgements
This work was supported by CNRST, National Center of Scientific and technical research

References

Optimizing the role of polymer blend, preparation and evaluation of Acyclovir controlled-release tablets by wet granulation technique

Barkat Ali Khan

Faculty of Pharmacy, Gomal University, Dera Ismail Khan 29500, Khyber Pakhtunkhwa, Pakistan

Abstract:

Aim and Background: This study was carried out to formulate and evaluate controlled release (CR) matrix tablets of Acyclovir using combination of hydrophilic and hydrophobic polymers. Acyclovir is a guanine derivative and is its half-life is short hence administered five times a day using immediate release tablets.

Methods: The role of Ethocel and Carbopol in formulation and evaluation of controlled release polymeric tablets of Acyclovir was investigated. Six formulations (F1-F6) were developed using Ethocel and Carbopol in equal combinations at drug-polymer (D: P) ratio of 10:5, 10:6, 10:7, 10:8, 10:9 and 10:10. Solubility study was performed using six different solvents, distilled water, 0.1 N HCl solution and 0.1N NaOH solution, phosphate buffer having pH 7.4, 7.2 and 6.8. The compatibility studies were carried out using FTIR and DSC. According to USP, Quality Control and dimensional tests (hardness, friability, disintegration and thickness) were executed. For in-vitro drug release studies of Acyclovir, dissolution studies was used using 0.1 N HCl medium at constant temperature of 37 ± 0.5 ºC. In order to analyze the drug release kinetics, five different mathematical models were applied to the release data.

Results: The results showed that there was no incompatibility between drug and polymers. Non-Fickian in-vitro drug release mechanism was found.

Conclusion: A formulation developed using blend of polymers, showed excellent retention and desired release profiles thus providing absolute control for 24 hrs. This study reduces the dose frequency of acyclovir from 5 times a day to once a day for the 1st time.

Keywords: Acyclovir, Carbapol, Ethocel
Health Monitoring by Automated Probe Handling, Microscopic Imaging and Image Interpretation System – A System for Airborne Fungi Identification

Petra Perner

1Institute of Computer Vision and Applied Computer Sciences IBaI, Arno-Nitzsche-Str. 45, Leipzig, 04277, Germany

*Corresponding author. Tel: (+49) 341 8612273; Fax: (+49) 341 86 12 275; E-mail: pperner@ibai-institut.de

Abstract

Human beings are exposed every day to bioaerosols in the various fields of their personal and/or professional daily life. The European Commission has rules protecting employees in the workplace from biological hazards. Airborne fungi can be detected and identified by an image acquisition and interpretation system. In this talk we present results on the development of an image interpretation system for airborne fungi identification. We explain the application domain and describe the development issues. The development strategy and the architecture of the system are described. Finally we give recent results.
Keywords: Microscopic image acquisition, microbiological probe handling, image analysis, image interpretation, case-based object recognition, case-based reasoning

Acknowledgements
The research work described was financed by the German Ministry of Economy BMWI under the grant number 16IN0147. It is a pleasure to thank the industrial partners for supporting this project.

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Protective Effects of Pomegranate Peel Extract on Cardiac Muscle in Streptozotocin-Induced Diabetes in Rats

Ashraf Y Albarakti

Human Anatomy department, College of Medicine, Taif University, Saudi Arabia

ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder in which the carbohydrate and lipid metabolism is improperly regulated by insulin. Diabetes has been recognized to be one of highly risk independent factor for cardiovascular disorders, cardiomyopathy, coronary heart disease, congestive heart failure, peripheral arterial disease and stroke. Pomegranate considers a native fruit of Al-Taif region. Pomegranates contain numerous of antioxidant polyphenolic substances as compared to other fruits and vegetables. Polyphenols have been shown to be cardio protective in different model systems. The present study has been designed to demonstrate the protective effects of pomegranate peel extract against diabetic heart complications in streptozotocin (STZ)-induced diabetic rats. Method: Sixty adult male albino rats weighing 250 – 300 gm, were used in this study and divided into three groups; the first group, normal group; the second was subjected to induction of diabetes; the third group was treated with pomegranate extract orally. At the end of the trial (8 weeks), animals heart specimens were taken after the last injection and processed for histological and ultrastructural studies. Results: Biochemical studies showed increased values of glucose, and cardiac enzymes (Troponin I and CK-MB) and myoglobin in the second group while in the third group there was improvement in values of the examined parameters. Histopathological studies revealed obvious many degenerative changes that were varying from vacuolation to myocytolysis and loss of myofibrils. Ultrastructural examination showed extensive degeneration of the muscle fibers with marked loss and even complete disappearance of myofibrils, with degeneration of many mitochondria. The toxic effects of diabetes on the myocardium were markedly attenuated by pomegranate extract administration in combination with streptozotocin-induced diabetic injections. Conclusion: From this study, it was concluded that, pomegranate peel extract administration markedly attenuated diabetes induced cardiomyopathic changes.

Keywords: pomegranate, diabetes, cardiac muscle, STZ, histopathology
Diabetes diagnosis through human respiratory using field emission of Al:ZnO nanorods

Marziyeh Advand, Mohammadreza Kolahdouz*, Mehrnoush Mahmoudian, Abbas Rostami, Fatemeh Salehi

School of Electrical and Computer Engineering, University of Tehran, Tehran, Iran

Sensor performance for acetone gas detection in expiration

Abstract

Sensing acetone gases with high sensitivity, selectivity and accuracy plays a vital role in the diabetes diagnosis from human respiratory. Detection of very skimp concentrations of acetone gas with low power expenditure is crucial. Field emission (FE) mechanism with exponential dependence of current on the applied voltage has converted this process to the method of choice with potentially high precision results. ZnO nanorods (NRs) FE has attracted so much attention because of ZnO exclusive specifications such as high chemical sensitivity, one dimensional electrical transport and biocompatibility [1]. The ZnO nanorods characteristics including doping and aspect ratio were optimized to decrease the emission power of the ZnO array. The grown array made up of ZnO NRs was coated with polypyrrol which is a kind of conductive polymers that absorbs acetone molecules [2], and in turn the molecules create a potential barrier on the tip of NRs. This potential barrier changes in absence or presence of acetone on these molecules. This phenomenon reduces the current density and the amount of current change can be used to extract the acetone concentration and blood glucose value.

Keywords: ZnO nanorods; field emission; diabetes examination; conductive polymer.

Reference


Development of a novel wound healing spray: soluble beta-1,3/1,6-glucan as an active ingredient in Carbopol matrix in a db/db wound model

Jostein Grip\textsuperscript{1,2*}, Rolf Engstad\textsuperscript{1}, Ingrid Skjæveland\textsuperscript{1}, Nataša Škalko-Basnet\textsuperscript{2}, Ann Mari Holsæter\textsuperscript{2}

\textsuperscript{1} Biotec Betaglucans AS, 9019 Tromsø, Norway
\textsuperscript{2} Drug Transport and Delivery Research Group, Department of Pharmacy, Faculty of Health Sciences, University of Tromsø The Arctic University of Norway, 9037 Tromsø, Norway

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Inclusion of Carbopol 971P NF, glycerol and soluble β-1,3/1,6 glucan in a hydrogel formulation for spray application for hard-to-heal wounds tested in diabetic mice (db/db).
Abstract

Chronic wounds represents a significant health problem worldwide. An older population is emerging and an increase in diabetes prevalence is reported globally. In the US alone there are over 6 million people affected by chronic or stalled wounds, which, if left un-treated, can lead to amputation of affected limb, decreases patient life quality or even death. There is a need for advanced wound healing products that can increase patient comfort, reduce healing time and lessen the economic burden on the healthcare system. Advanced wound care products to move chronic wounds from a stalled phase to a healing phase can be expensive, have low efficacy or both. The use of beta-glucan containing products have shown good safety profiles and an increase in healing rates in a phase II study with the soluble beta-1,3/1,6- glucan (βG).

The aim of this study was to develop a βG containing hydrogel, to potentially be used on chronic and burn wounds. Carbopol 971P NF (Carbopol) was chosen as the thickening agent, due to several attractive characteristics such as; low viscosity, low toxicity, high transparency and good ion toleration. Four different hydrogel formulations were prepared; LowβG (0.5% (w/w) Carbopol/0.25% (w/w) βG), MediumβG (0.5% (w/w) Carbopol /0.5% (w/w) βG), HighβG (0.25% (w/w) Carbopol/1.0% (w/w) βG) and Carbopol alone (Carbopol 0.5% (w/w)). First part of the study focused on characterization of the hydrogels by rheology and fluid affinity testing. The results showed that the formulations containing Carbopol alone or in combination with βG did not deteriorate over 26 weeks, and the fluid donation and absorption study determined that all hydrogel formulations have a donation profile which favors healing of dry wounds. The efficacy of the formulations, in vivo, using genetically diabetic mice (BKS.Cg-m Dock7m +/+ Leprdb /J), showed that Carbopol alone is less effective than the water control. High dose inclusion of the active ingredient βG, increases the epithelialization and wound contraction in the db/db mice. The positive effect of βG was not sufficient to counteract the adverse effect of Carbopol, therefore a more suitable thickening agent should be investigated for further development of a βG-sprayable wound care product.

Keywords: beta-glucan; Carbopol; db/db mice, rheology; hydrogel; wound healing

Acknowledgements

The authors would like to thank The Research Council Norway for funding under the grant number 240123/O30.
PREPARATION AND CHARACTERIZATION OF TERNARY COMPLEXES OF GLICLAZIDE WITH HYDROXYPROPYL-β-CYCLODEXTRIN AND SODIUM TAUROCHOLATE

Muhammad Tayyab Ansari, Mukhayar Aziz

1Department of Pharmacy, Bahauddin Zakria University, Multan, 60800, Pakistan

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Abstract

Purpose of research: To Enhance solubility and in vitro bioavailability (Dissolution) of Gliclazide (Anti-diabetic drug) along with hydroxypropyl-β-cyclodextrin and sodium taurocholate.

Experimental procedures: Ternary complexes were prepared by physical mixing (PM), kneading method (KM) and solvent evaporation (SE) techniques by using gliclazide, hydroxypropyl-β-cyclodextrin (HP-β-CD), and sodium taurocholate (STC) at drug, polymer (HP-β-CD), and sodium taurocholate ratios 1:1:1, 1:4:1, 1:7:1, 1:9:1 respectively. Complexes were evaluated by solubility, dissolution, Release kinetics models. These were characterized by Differential Scanning Calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), X-ray Diffraction (XRD), Scanning Electron microscopy (SEM).

Summary: GLC-(HP-β-CD)-STC complexes prepared by KM showed highest aqueous solubility (33.7 times) and dissolution rate (14.5 times) compared to Gliclazide followed by SE, PM respectively. Dissolution data was best fit by First order kinetics and release mechanism was Fickian type. FTIR spectra exhibited bonding interactions among Gliclazide and HP-β-CD in all ternary complexes except at 1:1:1 ratio. Complexes showed gradual decrease in intensity and peak broadening with rise in cyclodextrin content. All preparations produced unaltered bands of sulfonyl and amide carbonyl stretching vibrations of Gliclazide. Sodium taurocholate did not produce chemical interaction with others. XRD patterns revealed decreased intensity in SE and PM complexes but synergistic increase in intensity and more displaced angles were observed in KM complexes. DSC thermograms revealed decreased melting temperature of gliclazide in ternary complexes. Melting endotherm of gliclazide was lowest in KM followed by SE, PM. SEM showed smallest particle size in KM complexes compared to others while hydroxypropyl-β-cyclodextrin shape particles were observed in SE complexes.

Conclusions: Drug content studies, FTIR spectroscopic studies, X-Ray Diffractometry studies, Differential Scanning Calorimetry, Scanning Electron Microscopy and in vitro dissolution study data indicated that ternary complexes prepared by kneading method in 1:9:1 ratios were suitable for improving the solubility and dissolution of gliclazide.

Keywords: Gliclazide, Hydroxypropyl-β-Cyclodextrin, Sodium taurocholate, Ternary Complexes, Dissolution

Acknowledgements
Authors acknowledge the financial support of Higher Education Commission (HEC) of Pakistan for granting Research project No. Project No.20-1251/R&D/08 due to which this research was possible.

Reference
Functionalized graphene hybrids as highly targeted drug delivery carriers towards choroidal melanoma

Suyan Shan, Bingxin Zhao, Mimi Lin, Lu Yan, Karen Dong, Yong Liu

Laboratory of Nanoscale Biosensing and Bioimaging
School of Ophthalmology and Optometry
Wenzhou Medical University
Wenzhou, Zhejiang 325027, China

Abstract
Choroidal melanoma (CM) is one of the most deadly adult intraocular malignant tumors. Generally CM was dealt by clinical surgery. Secondary damage and even irreversible damage (e.g. loss of the eyeball) to the patients were inevitable. Chemotherapy has been considered as a more suitable alternative for therapy of CM. The traditional chemotherapy drugs, however, are suffered to pass through the so-called Corneal Barrier (CB) and targeted delivery ability to the tumor cells. In this work, we present our recent efforts on nanocarriers from polyethylene glycol modified hydroxylated graphene (PEG-GOH) which show superb performance on passing through the CB and targeted delivery towards OCM-1 cells (a typical cell line of CM). GOH with unique size and huge surface area was synthesized by our recently discovered edge-functionalized ball milling techniques. The as-synthesized GOH exhibited good ability to pass though cell membranes without any damage on cells. Particularly interesting, GOH tended to accumulate around tumor cells due to its slightalkalinity associated with -OH functional groups which were more attractive for the relatively acidic tumor cells than the normal cells. Furthermore, PEG was incorporated to further improve biocompatibility of the drug carriers and targeted ability towards tumor environment. Typical antitumor drug doxorubicin (DOX) was loaded onto the resulting PEG-GOH. For the purpose of comparison, normal ocular cells (ARPE-19) and tumor cells (OCM-1) were co-cultured in a Transwell assay with the addition of the as-prepared PEG-GOH/DOX. A 10% OCM-1 cell viability was obtained after 48 h while more than 50% ARPE-50 cells survived, suggesting excellent targeted suppressing ability of the resulting PEG-GOH/DOX towards tumor cells. This result was further confirmed by using an in vitro 3D tumor model which decreased two times more with PEG-GOH/DOX than that cultured with the pristine DOX.

Keywords: Graphene, Choroidal melanoma, Drug delivery, Doxorubicin (DOX)
Synthesis and optimization of Magnetic nanoparticles drug delivery by response surface

Fariba Tadayon1*, Mahdi Eshtiagh1, Ateke Tadayon2

1Department of Chemistry, North Tehran Branch, Islamic Azad University, Tehran, Iran
2Department of Biological Sciences, Tarbiat Modares University, Tehran, Iran

Abstract
Magnetic nanoparticles (MNPs) of targeted drug delivery were employed for some drugs including omeprazole and metronidazole in peptic ulcer disease and gastric cancer. This study focused on the potential of silica-coated magnetic nanoparticles (SiO2-MNPs) as a kind of Nano carrier gastric cancer and peptic ulcer therapy. SiO2-MNPs used in the targeted therapeutic delivery of omeprazole and metronidazole were prepared by a combined technique consisting of controlled precipitation and hydrothermal methods. Response surface methodology (RSM) was carried out in order to evaluate the efficiency of the SiO2-MNPs. Silica and amine groups in the coated nanoparticles were loaded to target drugs. The omeprazole and metronidazole were encapsulated by means of a silanizing agent with a surface rich in 2-aminopropyltrimethoxysilane layered around the SiO2-MNPs. For the identification and determination of the size and structure of nanoparticles techniques including infrared spectroscopy (FTIR), X-ray diffraction (XRD), (VSM) and scanning electron microscopy (SEM) were used.

Keywords: Magnetic Nanoparticles; Drug Delivery; Omeprazole; Metronidazole

Reference:

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Cytochrome P450 4A14, a target for the treatment of renal fibrosis

Yunfeng Zhou\textsuperscript{1*}, Rong Cao\textsuperscript{2}, Youfei Guan\textsuperscript{1}

\textsuperscript{1}Shenzhen University Health Science Center, Shenzhen, 518060, China
\textsuperscript{2}Department of Nephrology, the First Affiliated Hospital of Shenzhen University, Shenzhen, 518060, China

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- Angiotensin II
- MAPK signaling pathway
- TS-011
- Renal CYP4A14 expression
- 20-HETE production
- RPTCs collagen production
- TGF-β expression
- Renal fibrosis

Abstract

Angiotensin II (AngII) plays an important role in the pathogenesis of hypertension and associated cardiovascular and renal injuries. The aim of the present study was to elucidate the molecular mechanism by which AngII induces renal damage. We found that cytochrome P450 4A14 (CYP4A14) was significantly induced by AngII in the kidneys of mice, which was associated with a marked increase in blood pressure and proteinuria. We also demonstrated that CYP4A14 expression was predominantly upregulated in the proximal tubules of AngII-infused mice. Renal production of the major CYP4A14 metabolite, 20-hydroxyeicosatetraenoic acid (20-HETE), was also significantly increased in the AngII-treated mice. Compared to wild-type (WT) mice, CYP4A14 knockout (CYP4A14\textsuperscript{−/−}) mice exhibited significantly lower levels of blood pressure, renal 20-HETE production, proteinuria and renal fibrosis following AngII infusion. Furthermore, AngII-induced expression of profibrotic genes, such as collagen I and TGF-β, and proinflammatory genes, including MCP-1, TNF-α, IL-1 and IL-6, was significantly attenuated in the kidneys of CYP4A14\textsuperscript{−/−} mice. In vitro studies using renal proximal tubule cells (RPTCs) demonstrated that AngII significantly induced CYP4A14 expression and 20-HETE production via the MAPK signaling pathway. Treatment with AngII also resulted in a marked increase in TGF-β and collagen expression, which was attenuated by the CYP4A inhibitor TS-011. Collectively, these findings suggest that attenuated renal fibrosis in AngII-treated CYP4A14\textsuperscript{−/−} mice result from both reduced systemic blood pressure and renal 20-HETE production. Therefore, CYP4A14 may represent a useful target for the treatment of AngII-associated renal damage.

Keywords: cytochrome P450 4A14; angiotensin; fibrosis.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (81100611 to Zhou Y, 81390351 and 81270275 to Guan Y), the Natural Science Foundation of Guangdong Province (2014A020212423 to Zhou Y), the Foundation of Shenzhen Basic Research Project (JCYJ20150324141711629 to Zhou Y).
SNORD126 promotes hepatocellular carcinoma and colorectal cancer cell growth by activating the PI3K-AKT pathway through FGFR2

**Liang Chu** ¹, Xianlong Fang², Dongmei Yang², Hongping Luo¹

¹Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China.
²State Key Laboratory of Cell Biology, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, China.

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SNORD126

FGFR2 → PI3K → AKT → mTOR → Cell growth

Abstract

Small nucleolar RNA (snoRNA) dysfunctions have been associated with cancer development. SNORD126 is an orphan C/D box snoRNA that is encoded within introns 5-6 of its host gene, cyclin B1-interacting protein 1 (CCNB1IP1). The cancer-associated molecular mechanisms that are triggered by SNORD126 are not fully understood. Here, we demonstrate that SNORD126 is highly expressed in hepatocellular carcinoma (HCC) and colorectal cancer (CRC) patient samples. SNORD126 increased Huh-7 and SW480 cell growth and tumorigenicity in nude mice. Knockdown of SNORD126 inhibited HepG2 and LS174T cell growth. We verified that SNORD126 was not processed into small RNAs with miRNA activity. Moreover, SNORD126 had no significant expression correlation with CCNB1IP1 in HCC samples and did not regulate CCNB1IP1 expression. Our gene expression profile analysis indicated that SNORD126-up-regulated genes frequently mapped to the PI3K-AKT pathway. SNORD126 overexpression increased the levels of phosphorylated AKT, GSK-3β and p70S6K and elevated fibroblast growth factor receptor 2 (FGFR2) expression. siRNA-mediated knockdown or AZD4547-mediated inactivation of FGFR2 in SNORD126-overexpressed Huh-7 cells inhibited AKT phosphorylation and suppressed cell growth. These findings indicate an oncogenic role for SNORD126 in cancer and suggest its potential as a therapeutic target.

**Keywords:** Small nucleolar RNA; HCC; CRC; FGFR2; PI3K-AKT

Acknowledgements

This work was supported by National Natural Science Fund (31301064, 31671348, 81372453); Natural Science Foundation of Shanghai (13ZR1446300); Youth Innovation Promotion Association, Chinese Academy of Sciences (2013KIP101) and Shanghai Municipal Science and Technology Commission Fund (15431902800).
Type II diabetes and personality; a study to explore other psychosomatic aspects of diabetes

Maryam Esmaeilinasab, Mehdi Ebrahimi, Mohsen Heidari Mokarrar, Leila Rahmati, Mohammad Yoosef Mahjouri and Seyed Masoud Arzaghi*

Fellowship in Psychosomatic Medicine, Elderly Health Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Background
As one of the most common chronic diseases, diabetes and its control are affected by the patients’ psychological and spiritual attributes. The present study investigates the relationship between glycemic control in patients with type II diabetes and personality traits, defense mechanisms and spirituality.

Method
The present cross-sectional study was conducted on 400 Iranian patients with type II diabetes, 64% were men. Participants completed the NEO Personality Inventory, the Defense Style Questionnaire (DSQ) and the Spiritual Assessment Inventory (SAI) and then underwent a blood sampling for the assessment of HbA1C levels.

Results
Of the five personality traits, extraversion \( (r = -0.13 \text{ and } P < 0.01) \) and conscientiousness \( (r = -0.13 \text{ and } P < 0.01) \) had significant negative relationships with HbA1C levels, while neuroticism had a significant positive relationship with HbA1C levels \( (r = 0.12 \text{ and } P < 0.05) \). Of the defense styles assessed, the neurotic style was found to have a significant negative relationship with HbA1C levels \( (r = -0.1 \text{ and } P < 0.05) \). Also, of the spirituality elements, impression management had significant relationship with glycemic control \( (r = 0.17 \text{ and } P < 0.001) \).

Conclusion
According to data, Extraversion and conscientiousness can help control blood sugar while anxiety and negative emotions have detrimental effects on glycemic control. As a result considering psychological counselling beside medical interventions can help to better treatment.

Keywords
Personality traits Defense styles Spirituality Glycemic control Type II diabetes

Mohammad M. Agha,1,2,3,5*, Richard H. Glazier,1,2,4,5,7, Rahim Moineddin,1,2,4 Gillian L. Booth 1,2

1 Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada
2 Centre for Research on Inner City Health, St. Michael’s Hospital, University of Toronto, Canada
3 Paediatric Oncology Group of Ontario, University of Toronto, Toronto, Canada
4 Department of Family and Community Medicine, University of Toronto, Toronto, Canada
5 Dalla Lana School of Public Health, University of Toronto, Toronto, Canada
6 University of Toronto, Department of Medicine, Toronto, Canada
7 Department of Family and Community Medicine, St. Michael’s Hospital, Toronto, Canada

Abstract

Pregnancy in women with diabetes mellitus is associated with an increased risk of congenital malformations. More than 20 years ago, Europe countries signed a declaration agreed on a goal “Achieve pregnancy outcome in the diabetic woman that approximates that of the non-diabetic. The objective of the current study is to compare the trend over time of prevalence of congenital abnormalities among women with and without diabetes, and to explore the impact of food fortification.

Methods: Using health number and through record linkage, children born in Ontario to mothers with and without Diabetes between 1994 and 2007 were followed for the diagnosis of congenital anomalies. Adjusted rates and multivariate models were used to compare trends among children born in two groups.

Results: The birth prevalence of all anomalies combined is about 44% higher among children born to mothers with diabetes, this ratio observed minor fluctuation during the study period. While the gap between two groups of mothers remained unchanged for heart defects, the prevalence of brain defects among children born to mothers with diabetes observed a sharp decline. Due to increasing trend in the incidence of diabetes, we need to be more active and aggressive in implementing preventive measures.

Keywords: Diabetes, Congenital Abnormalities, Folic Acid
Engineering Dual-tagged Transmembrane Reporters for Exosome Tracking

Stacie Lin¹, Natalie Duong, Curley Kevin¹, Mai Anh Do¹, Grace Ling¹, Biao Lu¹

¹Department of Bioengineering, Santa Clara University, Santa Clara, CA95053, USA

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Abstract

Exosomes are potent nano-sized vesicles that can shuttle a large amount of bioactive cargos including proteins, lipids, and nucleic acids between cells. Due to their superior tissue-penetrating ability, exosomes offer opportunities towards of drug delivery to central nervous system and deep-seeded cancer cells. To realize this potential, engineering tools for exosome modifications must be invented in order to advance basic research and clinical translation. Here we report a development of novel dual-tagged transmembrane reporters that enable exosome tracking in living mammalian cells. By reconfiguring of exosome surface marker CD63, we generate two topologically distinctive scaffolds that allow flexible fusion of protein tags for both exosome detection and visualization. We show that these fusion proteins retain their ability to correctly target and participate into exosomes in a number of mammalian cells. We further demonstrate that the dual-reporters are useful in monitoring the biogenesis and secretion of exosomes in real-time. Our study highlights the potential of dual-tagged reporters for exosome tracking and opens up fresh opportunities for exosome-based applications such as exosome imaging, biologic-loading and therapy.

Keywords: exosome; drug delivery; nano-particle, GFP

Acknowledgements

This work was supported partly by funds from School of Bioengineering, the Willem P. Roelandts and Grant and the Kueller Research Program at SCU

Reference

Smad3 is essential for the development of type 2 diabetic kidney disease

Xiao R. Huang, Bi H. Xu, Yong K. You, Si F. Sun, Ronal CW. Ma, Hui Y. Lan

Department of Medicine and Therapeutics, Li Ka Shing Institute of Health Sciences, CUHK-Shenzhen Research Institute, The Chinese University of Hong Kong, China

Smad3 is a key signaling molecule and transcriptional factor of TGF-β signaling and has been shown to play a diverse roles in renal inflammation and fibrosis. However, the precise role of Smad3 in the pathogenesis of type-2 diabetic nephropathy remains largely unclear. Thus, in this study, we investigated the role of Smad3 in type-2 diabetes by genetic deletion of Smad3 from db/db mice. We first generated Smad3 knockout (KO)-db/db mice by crossing the db/m mouse to the Sma3+/- mouse. This cross-breeding resulted in five groups of mice: Smad3-/-db/db, Smad3+/+ db/db, Smad3+/-db/db, Smad3+/-db/m, and Smad3-/-db/m mice. Groups of 8 mice were scarified at weeks 8, 20, and 32 and fasting blood glucose, renal function, histological injury, and molecular pathology were examined. We found that compared to Smad3+/+db/m and Smad3-/-db/m mice that exhibited normal levels of blood glucose and urinary albumin excretion over the 32-week time course, Smad3+/+ db/db, Smad3+/+db/db developed progressive higher levels of fasting blood glucose (15-30mmol) with significant diabetic kidney injury including an increase in microalbuminuria and development of renal fibrosis. In contrast, deletion of Smad3 from db/db mice (Smad3-/-db/db) prevented the development of type-2 diabetes and diabetic kidney injury with normal levels of blood glucose and renal function without evidence for renal fibrosis and inflammation. In conclusion, Smad3 null mice are protected against the development of type-2 diabetes and diabetic nephropathy. These novel findings strongly suggest that Smad3 is essential transcriptional factor for the pathogenesis of diabetes and diabetic kidney complication.

Keywords: type-2 diabetes; diabetic nephropathy; Smad3; TGF-beta signaling

Acknowledgements
This study is supported by grants from Major State Basic Research development Program of China (grant no. 2012CB517705), Research Grants Council of Hong Kong (CUHK3/CRF/12R, TBS T12-402/13N).
CONUNDRUM OF RIGHT ATRIAL MASS

Dr S.S Bhattacharyya, Dr Y.R Shukla

Bombay hospital, 400020, Mumbai

Abstract

In the advanced stages of hepatocellular carcinoma (HCC), a tumor thrombus (TT) can form in the portal or hepatic vein. Extending to right atrium or presenting as budd-chiari syndrome. We report an unusual case of a patient who presented with complaints of breathlessness and syncope with no other significant past history. On investigation with no significant history in form of hepatitis or cardiovascular illness. On investigation USG abdomen revealed moderate ascites, mild splenomegaly with ivc thrombus extending to right hepatic vein, on CT scan of chest, abdomen and pelvis revealed thrombus in ivc and hepatic vein and enhancing mass in right atrium of size 3.5 by 4cm. on cardiac MRI right atrium mass 10 by 5 cm extending to ivc and right hepatic vein suggestive neoplastic origin. On PET scan, there no mass lesion showing uptake except for the right atrial mass, a CAG was also done which revealed tsvd, patient underwent surgery opcabg with excision of right atrial mass on cardiopulmonary bypass with total circulatory arrest, post operative histopathology revealed hepatocellular carcinoma. The review of literature was performed. This is first reported case in which patient presented with intra cardiac mass with no mass lesion in liver. The outcomes this case is to report this rare presentation of hepatocellular carcinoma with no primary liver lesion and its management.

Keywords: Right atrium mass, Case report, hepatocellular carcinoma, hcc with no primary liver lesion.

Reference

The Lifestyle Change after Initiating Basal Insulin in Insulin Naïve Patients with Type 2 Diabetes: Results from the ORBIT Study

Dongshan Zhu, MD; Heng Zhang, PhD; Xian Li, MD; Jiachao Ji, MD; Juming Lu, MD; Weiping Jia, MD; Linong Ji, MD; Puhong Zhang, PhD

1Diabetes Research Program, The George Institute for Global Health at Peking University Health Science Center, Beijing, P. R. China
2Biostatistics & Economic Evaluation Program, The George Institute for Global Health at Peking University Health Science Center, Beijing, P. R. China
3Department of Endocrinology, The General Hospital of the People's Liberation Army, Beijing, P. R. China
4Department of Endocrinology, Shanghai Sixth People’s Hospital, Shanghai, P. R. China
5Department of Endocrinology and Metabolism, Peking University People’s Hospital, Beijing, P. R. China

ABSTRACT

Based on a multicenter, registry study in China, we evaluated the changes in diet, physical activity (PA) and cigarette smoking in patients with T2DM after initiating basal insulins (BIs) for 6 months. Insulin naïve patients with T2DM aged 18-80 years uncontrolled on OAAs (HbA1c ≥7%, 53 mmol/mol) and willing to start BIs therapy were enrolled. Interviews were carried out at baseline and month 6. At each interview, the amount of diet intake, frequency of PA and smoking status were collected. A total of 12,353 patients who kept using BI during 6 months were analyzed. After 6-month follow up, the proportion of patients with higher (0.35-0.4 kg and above) and lowest (0-0.1 kg) daily staple food intake levels declined by 3%-4%, while the proportion of moderate (0.25-0.3 kg) consumption level increased by 9.3%. The overall level of daily intake of vegetable increased while fruit intake dropped evidently (a reduction from 0.05 to 0.25kg). No striking changes were observed on the meat intake except the highest intake level decrease slightly. Patients spent more days on PA (5.8 vs. 5.3days), and both proportion of patients with smoking (20.0% vs. 22.9%) and number of cigarette smoked per day declined (14.7 vs. 17.4). Changes of lifestyle factors were showed in Figure 1. Adding-on BIs therapy is associated with positive lifestyle change. Further studies are needed to establish the causal effect.

Key words: Lifestyle, Basal insulin, Type 2 Diabetes, Diet, Physical activity.
Prevalence of Prediabetes in Mexico

Sergio Islas-Andrade, MD, PhD, Maria Cristina Revilla-Monsalve, MsC, PhD, Fernando Guerrero-Romero MD, PhD, Marta Rodríguez MD, PhD, Jorge Escobedo de la Peña, Manuel González MD, MsC, PhD, esperanza Martínez Abundis, MD, MsC, PhD, Silvia E. Flores-Martínez MsC, PhD, Ricardo Perez Fuentes MD, PhD, Jose Sanchez Corona MD, MsC, PhD

MexDiab Group. Mexico City. CP: 06725

Epidemiological data on impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) based on a representative Mexican sample are available in this survey. In this study were to determine the prevalence and distribution of IFG and IGT, and to establish its relationship with obesity and Metabolic Syndrome in Mexican adults.

Methods: We performed a cross-sectional population-based study on a representative sample of Mexican adults aged 30 to 65 years. A total of 3,272 subjects, 1734 (53%) women and 1537 (47%) men, were included. Anthropometric measurements of obesity that included waist circumference (WC) and total body fat percentage were collected and the body mass index calculated. All subjects also underwent an oral glucose tolerance test. Diagnosis of glucose disorders was based on criteria of the American Diabetes Association.

Results: Prevalence of IFG, IGT, and IFG-IGT was 26.6%, 8.7%, and 11%, respectively. The age-adjusted prevalence of IFG (50.5% and 51.5%), IGT (49.7% and 51.9%), and IFG-IGT (58.2% and 48.6%) was similar in men and women. Prevalence of obesity was 45.9% more often in women (49.7% versus 43.0%, P = 0.01). A total of 1047 (32.0%), individuals were overweight. The odds ratio (OR) between WC and IFG (OR 3.1, CI 1.4-9.7), IGT (OR 3.2, CI 95% 1.2-9.1), and IFG-IGT (OR 2.8, CI 1.3-8.2) was higher than the OR of other measurements of obesity. 95%

Conclusions: Prevalence of prediabetes in the Mexican adult population is high. WC is the measure of obesity more strongly associated with metabolic glucose disorders. A high proportion of subjects with normal weight exhibit prediabetes. These data suggest that the Mexican population has an elevated risk for the development of metabolic and cardiovascular disease.

Keywords: Prediabetes, Obesity

REFERENCES


A 36-year old renal transplant recipient female with leg ulcer: a case report

Ali Monfared1*, Hojat Eftekhari2, Seyed Alireza Mesbah3, Abbas Darjani2, Seyyede Zeinab Azimi2

1 Urology Research Center, School of Medicine, Razi hospital, Guilan University of Medical Sciences, Rasht, 4144895655, Iran
2 Department of Dermatology, School of Medicine, Razi hospital, Guilan University of Medical Sciences, Rasht, 4144895655, Iran
3 Razi Pathobiology Laboratory, Razi hospital, 4143714713, Iran

Abstract

Introduction: Opportunistic infections are common in organ transplant recipients. After 6 months of transplantation patients have the highest risk of opportunistic infections such as cryptococcosis.

Methods: The report presents the case of a 36-year-old female renal transplant recipient transplanted 15 years ago with complain of few subcutaneous painful and warm nodules and large, warm, erythematous plaques on the mildly edematous right leg and ankle since one month ago. There was no systemic involvement. Laboratory data showed anemia with elevated level of creatinine (2.5 & 1.5) and blood urea nitrogen. Cyclosporine was changed to rapamune 1 mg/day, vancomycin and ceftazidim were prescribed for bacterial superinfection. Her condition deteriorated and nodular lesions progressed to ulcers. Culture of the tissue of lesion revealed the yeast colonies. Then she was treated with conventional amphotericin B 50 mg/day and oral fluconazole 200 mg/BD (adjusted due to renal function) subsequently.

Results: Skin biopsies showed the presence of chronic panniculitis associated with round yeast forms. A skin biopsy taken from a lesion which was treated with amphotericin revealed the yeast colonies. Tissue culture and DNA amplification: C. neoformans var. grubii. The serum cryptococcal antibody titer was 1:16. Chest radiography was normal. Examination of cerebrospinal fluid showed protein negative for cryptococcal antigen and there were no signs of intracranial hypertension.

The skin lesions regressed gradually and ulcers started healing, however leaving eschars. Black eschar remained persistent despite of fibrinolysin oint, administered topically; surgical debridement was carried out to remove the necrotic tissue and then graft was performed for her. The plan was to continue Fluconazole for at least 1 year.

Conclusions: Since the cryptococcal cutaneous lesions are often non-specific, the clinical picture solely is not enough to construct a definite diagnosis and there must be a high clinical suspicion. We need deep skin biopsy consisting of soft tissue to make the diagnosis of panniculitis. With only scraping the skin or aspiration material may identify fungal infection, but panniculitis would be missed. This may elucidate why only occasional case reports have revealed fungal panniculitis in post-transplant patients.

Keywords: cryptococcosis; renal transplant recipient, leg ulcer, nodule, panniculitis

Reference

Orbital Metastasis from Breast Cancer without Significant Changes in CT scan and MRI

Babak Hassanzadeh Rad*, Payam Azadeh and Ali Yaghobi Joybari

1Faculty of veterinary Medicine, Karaj Islamic Azad University, Karaj, 443356677, Iran
2Department of Radiation Oncology, Shahid Beheshti University of Medical Sciences, Tehran, 3322235678, Iran
3Department of Radiation Oncology, Shahid Beheshti University of Medical Sciences, Tehran, Postal code, Iran

Abstract

Orbital metastasis infrequently occurs in breast cancer; however breast cancer is the most common cause of orbital metastasis followed by lung, prostate, gastrointestinal tract, and skin (melanoma) cancers (1-3). Definite diagnosis of an orbital lesion includes an orbital biopsy (either FNA or open biopsy). However, in patients with known metastatic cancer, CT scan or MRI of the orbits can frequently show the presence of a mass, which often involves the orbital fat or extraocular muscles (4). On the other hand, these techniques may not completely reflect the metastases. Optical coherence tomography (OCT) is another method. It is a non-contact, non-invasive and high-resolution technique for imaging. There are two types of OCT, including time-domain (such as Stratus OCT3) and frequency-domain (same as Spectralis HRA+OCT). Frequency-domain is an advanced technique in imaging speed and diagnostic sensitivity. The Spectralis HRA+OCT produces a unique combination of retinal angiography and optical coherence tomography. Here, we report a case of orbital metastasis in a woman with previously diagnosed metastatic breast cancer presenting with visual disturbance of the right eye which was detected by optical coherence tomography. A 53-year-old woman presented with a 2-month history of diplopia and decreased vision in her right eye. Her past medical history included stage 2, hormone-receptor-positive and HER2-negative left breast carcinoma approximately 3 years prior to her presentation. She underwent modified radical mastectomy and axillary lymph node dissection. She subsequently received chemoradiation followed by hormonal therapy. Two years later, she presented with dyspepsia and abdominal pain. An abdominopelvic computed tomography (CT) scan showed ascites, peritoneal seeding, mucosal thickening, and partial obstruction in the proximal and distal part of the stomach, which was confirmed by endoscopy. In addition, ascites analysis was positive for malignancy. Chemotherapy was instituted which led to complete response. Six months later, she returned with complaints of headache and unilateral visual disturbance, including diplopia and decreased visual acuity in the right eye. Neurological examination failed to reveal any focal neurological deficit. Ophthalmologic examination revealed that the patient’s visual acuity was approximately no light perception (NLP) in the right eye. CT scan with and without contrast and magnetic resonance imaging (MRI) of the orbits and head were performed, which indicated no significant change. However OCT (Spectralis HRA+OCT) findings were most compatible with metastatic disease in vitreous and head of the optic nerve. OCT of orbital metastasis indicates a dome shaped elevation of the neurosensory retina and retinal pigment epithelium (RPE) with adjacent subretinal fluid. It could also be associated with retinal edema, intraretinal cysts, and thickening and detachment of the RPE. About 14.2% of cases have shown highly reflective points within neurosensory detachment. These points may correspond to retinal compromise by cancer cells or macrophages containing lipofuscin and melanin granules (5). In summary, increased vigilance on behalf of the oncologic and ophthalmologic communities is required when they observe symptoms and signs compatible with ocular disease in patients with an established diagnosis of breast cancer.

Keywords: Breast Cancer; Orbital Metastasis; CT scan; MRI.

Acknowledgements

We acknowledge Maryam Farasatinasab, Assistant Professor of Clinical Pharmacy, Iran University of Medical Sciences for manuscript and abstract finalization.

Reference

A Novel Drug Delivery Chip Design with IPMC as an Actuator

Matin Sadat Sanei Mousavi¹,², Amirhossein Karami², Mehrshad Ghasem Nezhad², Mostafa Masnadi², Faranak Manteghi², and Mohammadreza Kolahdouz²,*

¹ School of Chemistry, Iran University of Science and Technology, Tehran, Iran
² School of Electrical and Computer Engineering, University of Tehran, Tehran, Iran

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On/off mode of IPMC actuator as a capping material of the drug delivery chip used

Abstract

Ionic polymer metal composite (IPMC) is a smart electro-active polymer (EAP) which can be displaced using a very low electrical power. Nafion polymer as one of the electroactive materials acquires quit a lot of nano-channels in its structure. By the time that the H⁺ ions of its chemical structure replace with smaller and more active ions such as Na⁺ and Li⁺, they start moving in the channels in the applied electrical field direction and make the polymer to bend. The generated electrical current through the polymer is highly based on the quality of the electrode deposition on the nafion. Low and stable contact resistance plays an important role in transporting the carriers in the electronic circuit. Pt chemical deposition is one of the widely used methods to fabricate a composite of Nafion and layers of metal electrodes on it [1]. IPMC since merging has been widely used in many applications such as biomechanics, robotics, sensors and MEMS systems. The bio applications of IPMC has been widely studied due to its biocompatibility. One potential device in which IPMC has been used is the micro-pumps in the drug delivery chips [2-3]. However, due to its low movement power produce by applying bias, application as a micro pump and its ability to get the whole drug released at low Reynold numbers is still a challenging task and under negotiation. The typical force generated at the tip of the IPMC as a bending actuator is approximately 10 gf for a 45 × 15 × 0.35 mm IPMC strip. The bending deflection can be very large and could extend beyond 90°. Hence, IPMC is an actuator with large deflection but low force bending which can be operated with low excitation voltage [4]. Herein, a 20 × 4 mm² strip of IPMC synthesized by Pt chemical electrode deposition on Nafion (128 µm) as an actuator has that the top PDMS capping of the drug container which was attached to IPMC and let the whole drug released. The silicon single reservoir chip is also covered by a perforated PDMS layer on the top so that the two layers of the PDMS were completely attached to each other and sealed the reservoir at the off mode, when there is no electricity applied. By applying a low electrical voltage, the IPMC actuator bends upward and hence the two sealed PDMS layers separate from each other which led to the release of drug from the small cavity made in the lower PDMS layer.

Keywords: Ionic Polymer Metal Composite, silicon chip, PDMS layer

Reference

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Screening of interactions between Janus dendrimer coatings and drug nanocrystals

Markus Selin\textsuperscript{1*}, Luis M. Bimbo\textsuperscript{2}, Sami Nummelin\textsuperscript{3}, Leena Peltonen\textsuperscript{1}, Tapani Viitala\textsuperscript{4}, Jouni Hirvonen\textsuperscript{1}

\textsuperscript{1}Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, FI-00014, Finland
\textsuperscript{2}Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE, United Kingdom
\textsuperscript{3}BioHybrid Materials, Department of Biotechnology and Chemical Technology, Aalto University, FI-00076, Finland
\textsuperscript{4}Division of Pharmaceutical Biosciences, Faculty of Pharmacy, University of Helsinki, FI-00014, Finland

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| Nanomilling in stabilizer solutions | Characterization of stabilized drug nanocrystals, and physical interactions between stabilizers and model drug compacts | Computer modelling the results |

Process diagram towards computer screening of polymeric stabilizers for drug nanocrystals.

Abstract

In this research, we aim to establish a model for in silico screening of polymeric chemical structures intended for use as stabilizers for drug nanocrystals. Drug nanocrystals are utilized to improve the solubility of poorly soluble drug materials, and stabilizers are needed in order to prevent the aggregation of newly formed nanosized drug particles in suspension. In this study indomethacin was used as poorly soluble model drug material for nanocrystals and a set of novel amphiphilic Janus dendrimers were used as stabilizers. Typically surface-active agents or polymers are utilized as stabilizers for drug nanocrystals, but the novelty and benefits of Janus dendrimers utilized in this study are their modular structures, which enables for example easy addition of functional of targeting groups on formed particle surfaces. Janus dendrimer coated drug nanocrystals were produced by miniaturized pearl milling method, which demands only of few milligrams level of materials. Existing physicochemical analytical methods, including surface plasmon resonance (SPR), contact angle measurements, dynamic light scattering (DLS), differential scanning calorimetry (DSC), various spectroscopic techniques like Raman and FT-IR, X-ray diffraction, and scanning electron microscopy (SEM) techniques were utilized for thorough characterization of formed drug nanosystems. Based on the preliminary results, novel dendrimers were capable of stabilizing formed indomethacin nanocrystals; drug nanocrystal particles with approximated sizes of few hundreds of nanometers were formed successfully. When different Janus dendrimers with different amphiphilic structures were utilized, differences in formation of drug nanocrystals were seen. For more precise structure related analysis further screening is going on and also long time stability testing of nanosuspension are under study.

Keywords: Dendrimer, nanocrystal, coating, screening, modelling

Acknowledgements

Financial support by the Academy of Finland, Sigrid Juselius Foundation, Instrumentarium Science Foundation, Magnus Ehrnrooth Foundation, Biocentrum Helsinki, The Finnish Cultural Foundation, Orion Farmos Research Foundation and Jane and Aatos Erkko Foundation is gratefully acknowledged.
Predictors of initiating Basal-bolus Regimen in Type 2 Diabetes Patients with Uncontrolled Hyperglycemia by Oral Antidiabetic Drugs in China

Heng Zhang, PhD, 1 Puhong Zhang, PhD, 1 Dongshan Zhu, MD, 1 Xian Li, MD, 1 Jiachao Ji, MD, 1 Jianping Weng, MD, 2 Juming Lu, MD, 3 Xiaohui Guo, MD, 4 Weiping Jia, MD, 5 Linong Ji, MD*. 6

1The George Institute for Global Health at Peking University Health Science Center, Beijing, China.
2The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.
3Chinese PLA General Hospital, Beijing, China.
4Peking University People’s Hospital, Beijing, China.
5Shanghai 6th Hospital, Shanghai, China.

ABSTRACT

OBJECTIVE
To investigate the proportion of basal-bolus as the basal insulin (BI) initiation regimen and related factors among type 2 diabetes mellitus (T2DM) with insufficient glycemic control by oral antidiabetic drugs (OADs).

RESEARCH DESIGN AND METHODS
This was a sub-analysis of baseline data from the Observational Registry of Basal Insulin Treatment (ORBIT) program—a multicenter, observational prospective study based on a nationally representative sample of 18,995 insulin-naïve T2DM on OADs with a glycosylated hemoglobin (HbA1c) level ≥7% measured within 3 months in China. Proportion of different insulin initiation regimen and related factors of basal-bolus by different patient group (inpatient or outpatient) were analyzed.

RESULTS

Basal-bolus (plus OADs) accounted for 24.6% of the BI initiation regimen. Among patients with bolus insulin, 97.8% used a multiple daily injections (MDI) approach. Compared with outpatients (10.3%), a much higher proportion of inpatients (35.8%) initiated bolus insulin in addition to BI. Multivariable logistic analysis indicated that diabetes duration in years, number of complications in the past, and higher HbA1c level were positively associated with basal-bolus initiation, while number of OADs at baseline and usage of detemir and glargine as BI were inversely associated with basal-bolus initiation in both patient groups.

CONCLUSIONS

This study suggests that there is a delay of BI initiation in Chinese T2DM patients with suboptimal glycemic control by OADs, resulting in a high proportion of basal-bolus regimen at BI initiation, for which an overwhelming majority is using a MDI approach. Greater efforts are needed to motivate diabetes patients and physicians to strive for the recommended treatment goals in a timely manner.

Key words: Type 2 diabetes mellitus; basal insulin initiation; basal-bolus; insulin intensification; glycemic control.