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Mari Katsura, Biomed Res 2018, Volume 29 | DOI: 10.4066/biomedicalresearch-C2-006

EFFECTS OF LOW DOSE RADIATION ON DEVELOPING HUMAN RETINAL GANGLION CELLS FROM INDUCED PLURIPOTENT STEM CELLS

Mari Katsura
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Retinal ganglion cells (RGCs) are essential components for vision, whose long axons link to the visual field in the brain. Loss of RGC is often in the eyes observable in the eyes with various visual disorders, such as glaucoma and ischemia. Developments of RGCs start at gestational 5 weeks earlier than other kinds of neural cells in the retina. However, regeneration of RGC has never been reported in mammalian eyes so far. Instead, small amount of loss in RGC does not cause visual disturbance which may be supported by some surplus of RGCs in retina. To validate the effects of low dose radiation on the differentiation of RGC, we have established a protocol to differentiate iPS into RGCs within 35 days. We applied low dose irradiation of 30 mGy and 180 mGy for 24 hours from day 4 to day 5 and observed that the axagonal elongation was interfered. To dissect molecular mechanism of this finding, we performed a series of transcriptome analysis and extracted a group of genes, including PAX6, which were down regulated in a dose dependent manner. To identify radiation dependent gene regulation, we performed epigenetic analysis to identify active enhancers in affected genes. Based on H3K4me3 and H3K27ac localization, we work on motif analysis to identify consensus transcription factor binding sites could be observed. Currently, we are recollecting time course data and trying to find the earliest responsive transcription factor in low dose irradiation stimulation.

BIOGRAPHY

Mari Katsura is graduated from Hiroshima University Medical School, Hiroshima, Japan. She has been an ophthalmologist after graduation. Now her work is research for the effects of low dose radiation on human health, especially in neural cells. Her laboratory is in Isotope science center, The University of Tokyo, where many researchers from different fields are working cooperatively.

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MECHANISMS MEDIATING VASCULAR OCCLUSION IN THROMBOIN FLAMMATORY DISEASES: ROLE OF THIOL ISOMERASES

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Real-time intravital microscopic studies have provided compelling evidence that intravascular cell-cell aggregation directly contributes to vascular occlusion and tissue damage, a leading cause of morbidity and mortality of patients with cardiovascular diseases. In particular, platelet-leukocyte interactions on the activated endothelium are crucial for the initiation and progression of thrombotic and inflammatory diseases. Platelet-leukocyte adhesion is mediated mainly through the interactions of platelet P-selectin and glycoprotein Ibα with neutrophil P-selectin glycoprotein ligand-1 and αMβ2 integrin, respectively. Despite our knowledge of the major receptors and counter-receptors, it remains poorly understood how the receptor-counter-receptor interactions are controlled during cardiovascular diseases. Evidence is mounting that the function of plasma proteins and cell surface receptors involved in thrombosis and inflammation is controlled by oxidation or reduction of allosteric disulfide bonds. Thiol isomerases catalyze thiol-disulfide exchange and regulate protein folding and function. Intriguingly, despite having an endoplasmic reticulum retention signal, several thiol isomerases are released from intravascular cells and detected in the circulation and on the cell surface. We have demonstrated that the plasma level of protein disulfide isomerase (PDI), a prototypic thiol isomerase, is enhanced during thrombosis and vascular inflammation and that extracellular PDI plays a critical role in platelet-leukocyte aggregation under thromboinflammatory conditions. In this presentation, I will discuss the molecular mechanism by which PDI participates in the initiation and progression of thromboinflammatory diseases. A better understanding of the molecular basis of thiol isomerase-mediated cell-cell interactions will provide insights into the development of novel therapeutic agents for the prevention and treatment of cardiovascular diseases.

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CHANGES IN THE SYSTEMIC INFLAMMATORY RESPONSE AND RENAL FILTRATION FUNCTIONS USING A CLOSED CIRCUIT OF THE ARTIFICIAL CIRCULATION WITH CORONARY ARTERY BYPASS GRAFTING

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The objective of this report was to study the direct results of cardiopulmonary bypass surgery in conditions of cardiopulmonary bypass in closed and open circuits.

Methods: 2 cohorts of patients underwent coronary artery bypass grafting using open and closed CPB contours. Patients in group 1 (n = 50; mean age 65 ±4,2 years) underwent coronary artery bypass grafting in the closed CPB contour. Patients in group 2 (n = 50; mean age 64 ±5,3years) underwent coronary artery bypass grafting in the open CPB contour. Clinical characteristics of both cohorts were comparable. The total time of cardiopulmonary bypass was lower in the 1-st group than in the 2-nd group (58min±12,7 and 64min ±16,9, respectively; p = 0,04). The average number of grafts was 3 ±0,67 in the control group, 3 ±0,53 in the comparative group. Postoperative analysis of laboratory indicators has been divided into 2 stages at the time of six hours and sixteen hours.

Results: When comparing two groups on the expiration of 6 hours after operation level of leucocytes, platelets, C-reactive protein, urea and creatinine has not undergone a significant difference. After 16 hours of operation, the level of leucocytes was 10x109 ±13,2 and 11,3x109 ±2,4 (p= 0,02) respectively; the level of C-reactive protein was 4mg/dl ±2,8 and 5,6 mg/dl ±2,2 (p=0,01) respectively. There were no statistically significant changes in urea and creatinine levels in both groups.

Conclusion: The closed contour of cardiopulmonary bypass can be used effectively and safe for coronary artery bypass grafting surgery.

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BRIHH IN PATIENTS WITH DM REPERCUSSION AND DIAGNOSIS IN STUDIES OF MYOCARDIAL PERFUSION WITH SESTAMIBI

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It is known that the LBBH has different etiologies, among which, we must consider the obstructive coronary atherosclerosis, mainly in the anterior descending coronary artery, however, there have been no analyzes that specifically assess the presence of LBBH in diabetic patients and its Impact on myocardial perfusion studies with sestamibi. The purpose of this study is to know if the diabetic patient, with LBBB, will increase the probability that said blockade is related to obstructive coronary atherosclerosis, detected by myocardial perfusion studies, with sestamibi as a radiopharmaceutical. Additionally, the diagnostic accuracy of the study will be assessed to adequately characterize the absence or presence of CAD. In a retrospective way, 128 patients with LBBH were selected, sent to the nuclear medicine service from 2013 to 2016, with suspicion of CAD. Of these patients, 68 (41 women and 27 men, average age 65 years, age range of 54 to 88 years) had diabetes mellitus, among other known risk factors. The remaining 60 patients (36 women and 24 men, average age 69 years, age range of 54 to 88 years), suffered from other risk factors other than diabetes. The patients followed the protocol for the preparation and conduct of myocardial perfusion studies of the American guidelines. Patients without BRDHH were excluded. Stress tests of all patients were performed with dipyridamole. The reference test against which the results were compared, was therapeutic coronary angiography, in the patients who were found to have CAD by our method. And when the treating physician considered it, in patients without CAD by our method, coronary angiotomography was requested.Of the 68 patients with diabetes mellitus, 52 were found to have CAD and 16 without CAD. Of the 60 non-diabetic patients, 48 were found to have CAD and 12 without CAD. The chi square test was used to establish a relationship between the known variables (diabetes and branch block / non-diabetics and branch blockade, healthy and sick). The null influence of diabetes mellitus on the increase in CAD in patients with LBBH, was considered as a null hypothesis. The result was that such hypothesis was confirmed. Regarding the diagnostic accuracy of the nuclear medicine study in patients with diabetes, it was 94.1%, sensitivity of 94.2% and specificity of 93.8%. In non-diabetic patients, the diagnostic accuracy of the nuclear medicine study was 93.8%, sensitivity of 93.8% and specificity of 93.8%. In both cases, positive predictive values were found, above 97%.

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MINERALOCORTICOID RECEPTOR ANTAGONISM: NEW OPPORTUNITIES FOR CARDIOVASCULAR RESEARCH

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The steroidal Mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone have been shown to be effective in reducing mortality and hospitalizations for heart failure in patients with chronic HFrEF. Their role in patients with HFpEF remains controversial since the overall results of TOPCAT were equivocal. An analysis of geographic differences in TOPCAT have however suggested patients randomized from Russia and the Republic of Georgia did not have the mortality risk associated with prior epidemiological and randomized HFpEF studies and that many patients in these countries did not take assigned study drug. The Spirrit trial funded by the Swedish Heart foundation and the NHLBI is therefore currently randomizing > 3000 patients with a LVEF > 40% to spironolactone or placebo using an open label probe design with CV mortality as the primary endpoint . The steroidal MRA spironolactone has also been shown to be the agent of choice in patients with resistant hypertension (PATHWAY). There are however suggestions that MRAs may have an important role in patients with the metabolic syndrome and hypertension at an earlier stage . The Envoy trial ((n=300) will be evaluating patients with visceral obesity and hypertension and will compare the effectiveness of indapamide to spironolactone on top of amlodipine over a 1 year follow up. The use of the steroidal MRAs however is limited by the risk of hyperkalemia. New non nonsteroidal MRAs with a lower incidence of hyperkalemia than spironolactone are currently being investigated in patients with uncontrolled hypertension and an eGFR ,45-15 ml/min/1.73 m2 (N=240) as well as in patients with Diabetic Nephropathy (Figaro ,n=4000, Fidelio n=6000). The availability of these new nonsteroidal MRAs as well as new safe and effective K+ lowering agents such as Patiromer opens the possibility for the use of MRAs in high risk patients with CKD, Diabetes mellitus, heart failure and or hypertension.

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EVALUATION OF [^{64}Cu] PYRUVALDEHYDE-BIS (N4-METHYLTHIOSEMICARBAZONE) AN ATTRACTIVE RADIOPHARMACEUTICAL FOR MYOCARDIAL PERFUSION FOR PET

Juan C Manrique Arias
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Copper (Cu) is an important trace element in humans; Due to its decay characteristics, Cu-64 ($T_{1/2}$=12.7h, β^+ [17.4%], β^- [39%], E.C. [43.6%]) is an attractive radionuclide with applications in both, PET Copper molecular imaging and targeted therapy. This radionuclide has been widely used in the labelling of macromolecules such as peptides, proteins, monoclonal antibodies, and thiosemicarbazone complexes, [^{64}Cu]Cu(II)-pyruvaldehyde-bis(N_4-methyl-thiosemicarbazone) ([^{64}Cu]Cu(II)-PTSM), a tracer for myocardial perfusion, Cu-64 is produced via the ^{64}Ni(p,n)^{64}Cu, nuclear reaction. [^{64}Cu]-PTSM is prepared using in-house made PTSM ligand and [^{64}Cu] chloride. Radiochemical purity of [^{64}Cu]-Cu(II)-PTSM is higher than 98%. Cu(II) bis(thiosemicarbazone) complex as myocardial perfusion agents, labelled with positron emitters of Cu with half-lives suitable for its regional distribution from a satellite Centre.

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CABG IN DIFFUSE CORONARY ARTERY DISEASE

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Statement of the problem: In India 2.78 million death are due to Cardiovascular diseases of which 50 % are due to CAD. Peculiarities of CAD patterns in Indian patients- Younger age at presentation, high incidence of DVD and TVD, diffuse involvement, distal disease and significant LV dysfunction at presentation

Diffuse CAD: Length of significant stenosis > 20 mm, multiple significant stenosis (> 70% narrowing) in the same artery separated by segment of apparently normal vessel and significant narrowing involving the whole length of coronary artery.

Methodology: We in our institute, perform OP CAB and use LIMA and veins as conduits to perform the surgery. Once the conduits are harvested, we heparinize with I.V. Heparin 3 mg/Kg given to achieve an ACT >300.Using the octopus as stabilizer, we perform an endartrectomy of the LAD first and then use a vein patch to cover the defect. LIMA is then used to anastomose the LAD on the vein patch. Veins are used to bypass the LCX and RCA, as deemed appropriate. The proximal ends of the vein grafts are anastomosed to Ascending Aorta with side clamp and heart beating. Intra op we start Lomodex infusion 20ml/hr which is continued for 24 hours and the inotropes used are Adrenaline and Dobutamine as and when necessary. Postoperatively aspirin 75mg is given and Heparin infusion started after 6hours to maintain ACT of around 150 for 24 hours. Patients are usually extubated after 4 hours provided they are hemodynamically stable. Anticoagulation by Acitrom is commenced orally from day 1 to maintain an INR of 2 for 3 months.

Result: Out of the 20 patients in last 18months outcomes have been excellent with no in-hospital mortality or cerebrovascular incidents.

Conclusion: Off pump CABG with coronary end-arterectomy offers a good solution to the problem of diffuse coronary artery disease.

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NOVEL APPROACHES FOR ENDOGENOUS HEART REPAIR

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Background: Heart failure is often caused by loss of cardiac cells that are unable to re-enter the cell cycle for regeneration. Numerous attempts to identify such cell cycle regulators that could induce cell division of cardiomyocytes, or other cell types, have resulted in nuclear division (karyokinesis), but inefficient cleavage into two distinct daughter cells (cytokinesis) and subsequent survival. Such strategies stimulate cell cycle markers in no more than 1% of cardiomyocytes, limiting their utility.

Methods and results: Here, we took a combinatorial approach to screen for cell cycle factors and conditions that could recapitulate the fetal state of cardiomyocyte division. We found that ectopic introduction of the Cdk1/CyclinB1 and the Cdk4/CyclinD1 complexes promoted cell division in at least 15% of mouse and human cardiomyocytes *in vitro*. Rigorous assessment of cell division *in vivo* with the cardiac specific (-MHC) Cre-recombinase dependent Mosaic Analysis with Double Markers (MADM) lineage tracing system revealed similar efficiency in adult mouse hearts, leading to cardiac regeneration upon delivery of cell cycle regulators immediately after myocardial infarction and even one week after injury. This ability of cardiac regeneration resulted in significant improvement in cardiac function following acute or subacute myocardial infarction. Intra-myocardial injection of adenoviruses encoding the 4 cell cycle gene either injected at the time of the infarction or one week following myocardial infarction resulted in significant improvement in cardiac function as assessed by echocardiography and MRI compared to animals received control virus. Furthermore, chemical inhibition of Tgf and Wee1 made CDK1 and cyclin B dispensable, simplifying the minimal genetic requirement.

Conclusion: These findings reveal a discrete combination of genes that can unlock the proliferative potential in cells that had permanently exited the cell cycle.

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RESTRICTIVE HEART REMODELING AFTER COMPLEX THERAPY OF BREAST CANCER

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Breast cancer treatment complications, including cardiotoxicity are most dramatic in spite of the increased number of survivours in last decades. Major findings in those are the worsening of systolic function regarding LVEF calculation and deformational indices. Indeed, same patients demonstrate HF symptoms despite "normal" LVEF, which need to be investigated.

Aim: regular assesment of heart remodeling and function was performed to find a substrate of HF symptoms in patients under complex treatment of breast cancer. Cohort of 40 women (27-58 y.o.) with HER2+ breast cancer was assesed by ECG, Echo, biochemical blood markers every 3 months after initial diagnosis and beginning of treatment. Among them 40 pts had metastatic cancer, 5 - primary breast cancer. Radiotherapy, surgery and chemotherapy were performed from 6 months to 10 years before initiation of trastuzumab treatment. Cardiotoxicity (symptomatic falling of LVEF>10% versus basal data) was revealed in one woman, who was excluded from present study. Nine patients met HF symptoms (NYHA I-II) and were treated with iACE, sartans, ivabradine.

Results: Shortening of long axis and decreasing of volume of both atrial chambers followed by the increasing of sphericity indices of LA and RA in groups . Patients of groups of treatment had negative dynamics of systoilc longitudinal deformation of both ventricles (for both $p<0,05$). Decreasing of systolic deformation and restrictive chamber remodeling correlated to exercise intolerance and HF symptoms ($p<0,02$). No patients had decreasing of LVEF (pair t-test, $p>0,05$).

Conclusion: all patients demonstrated decreasing of atrial chamber short axis and volume. Less dramatic remodeling and HF symptoms were found in patients with monotherapy of trastuzumab. Atrial restrictive remodeling was revealed in patients treated subsequently by radiotherapy, anthracyclines and inhibitors of HER2neu+ receptors and followed by the worsening of ventricular systolic deformation and HF progress.

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THE ROLE OF DOBUTAMINE DOSE ON THE CARDIAC PARAMETERS

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Objectives: The report presents the effects of dobutamine dose on the cardiac parameters such as blood pressures (basal, systolic, diastolic & maximum), heart rates (basal, peak & maximum), baseline cardiac ejection fraction, and ejection fraction on dobutamine dose.

Background: There is a little literature about the effects of dobutamine dose on the cardiac parameters.

Materials and Methods: The effects of dobutamine dose on the cardiac parameters have been examined based on a real echocardiography stress data set, collected at University of California, Los Angeles on 558 patients with 31 explanatory variables/factors. The distribution of the considered cardiac parameters is gamma with non-constant variance. So, they have been analyzed by joint generalized linear gamma models.

Results: The mean basal blood pressure (BBP) decreases as the double product of maximum heart rate (MHR) & maximum blood pressure (MBP) at dobutamine dose (DPMAXDO) ($P<0.001$) increases, while the variance of BBP increases as the DPMAXDO ($P<0.001$) increases. The mean systolic blood pressure (SBP) increases as the dobutamine dose (DOSE) ($P=0.032$) increases, while the mean SBP increases as the DPMAXDO ($P<0.001$) decreases. Mean MBP increases with the increase in DPMAXDO ($P<0.001$). The mean baseline cardiac ejection fraction (BEF) decreases as the DOSE ($P=0.025$) increases. The mean ejection fraction on dobutamine dose (DOBEF) increases as the DOSE ($P=0.011$) increases, while the variance of DOBEF increases as the dobutamine dose at maximum double product (DOBDOSE) ($P=0.001$) decreases. The mean basal heart rate (BHR) increases as the DPMAXDO ($P<0.001$), or DOBDOSE ($P=0.074$) decreases. The mean peak heart rate (PHR), or maximum heart rate (MHR) increases as the DPMAXDO ($P<0.001$) increases, while the variance of PHR, (MHR) increases as the DOBDOSE ($P<0.001$) decreases (increases). On the other hand, dobutamine dose is associated with many cardiac parameters such as SBP, MBP, new myocardial infraction (new MI), history of MI (hxofMI) etc.

Conclusions: Only the dobutamine dose effects are observed on SBP, MBP, DOBEF, newMI, histMI, etc, while the joint effects of dobutamine (DPMAXDO and DOBDOSE) are observed on each cardiac parameter. The results are new inputs in the dobutamine dose study literature.

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PREVALENCE OF CORONARY ARTERY DISEASE DETECTED BY MYOCARDIAL PERFUSION SCINTIGRAPHY IN PATIENTS OF ESSENTIAL HYPERTENSION WITH OR WITHOUT DIABETES MELLITUS

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Purpose: Aim of this retrospective study was to find prevalence of coronary artery disease (CAD) in hypertensive patients with or without diabetes mellitus.

Materials and methods: Data of patients having essential hypertension (n=931) referred to PINUM for myocardial perfusion scintigraphy (MPS) was analyzed. This data was divided into two groups: HDM group contains data of patients having hypertension with diabetes mellitus (n=456, 48.9% of total, M: F=245:211). While data of patients having hypertension without diabetes mellitus was placed in H group (n=475, 51.0% of total, M: F=254:221). Mean age was 52.4 + 10.2years in HDM group and 48.7 + 10.9years in H group. Duration of hypertension was 5.2 + 5.0years in HDM group and 5.6 + 5.5years in H group. Duration of diabetes mellitus was 7.0 + 5.8years in HDM group. Each group was divided into subgroups based on gender, clinical presentation and age. Patients with perfusion defects on MPS were considered to have CAD.

Results: Prevalence of CAD is higher in HDM group than H group subjects (47.8% vs. 30.1%; p<0.001). Prevalence of CAD is higher in males than females in HDM (53.9 % vs. 40.8%) and H groups (39.4% vs. 19.5%) respectively. The difference of prevalence of CAD in HDM and H groups is more marked in females (40.8% vs. 19.5%; p<0.001) than males (53.9 % vs. 39.4%; p=0.001). Prevalence of CAD in patients with typical presentation is not statistically significant in HDM and H groups (72.3% vs. 68.4%; p=0.645), while in subjects with atypical presentation, prevalence is significantly higher in HDM than H group (40.8% vs. 26.8%; p<0.001).

Conclusion: Prevalence of CAD is higher in the HDM group than the H group. Prevalence of CAD is higher in males than females in both groups. Prevalence is almost similar in patients with typical presentation in both groups. While with atypical presentation, prevalence of CAD is significantly higher in HDM group. Prevalence of CAD increases with age in both groups. However in females, this increase in prevalence with age is markedly slower till the age of 65years. After 65, prevalence of CAD in females approaches to that in males.

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CLINICAL APPLICATION OF AUTOLOGOUS WHOLE BONE MARROW STEM CELL TRANSPLANTATION FOR CRITICAL LIMB ISCHEMIA WITH BUERGER'S DISEASE

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KoreaOur goal was to evaluate early results of the clinical application of autologous whole bone marrow stem cell transplantation (AWBMSCT) for critical limb ischemia (CLI) in patients with Buerger's disease. We retrospectively analyzed the data of 58 limbs of 37 patients (mean age, 43.0 years; range, 28-63 years; male, 91.9%) with Buerger's disease with CLI who were treated with AWBMSCT. We analyzed Rutherford category, pain score, pain-free walking time (PFWT), total walking time (TWT), ankle brachial pressure index (ABPI), and toe brachial pressure index (TBPI), and investigated wound healing and occurrence of unplanned amputations. The mean follow-up duration was 11.9±7.2 months (range, 0.9-23.9 months) and 100%, 72.4%, and 74.1% of patients were available to follow-up 1, 3 and 6 months after AWBMST, respectively. At 6 months, patients demonstrated significant improvements in Rutherford category (P<0.0001), pain score (P<0.0001), PFWT (P<0.0001) and TBPI (P<0.0001). ABPI was increased compared to baseline, but the difference was not significant. A total of 76.5% ischemic wounds achieved complete or improved healing. AWBMSCT is a safe and effective alternative or adjunctive treatment modality to achieve clinical improvement in patients with CLI.

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STENTS WITH GROWTH FACTOR SECRETING MSCS ENHANCED RE-ENDOTHELIALIZATION AND DECREASED RESTENOSIS IN SWINE MODEL

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Currently, cardiac stenting is the most effective and least invasive approach to treating the disease. However, in-stent restenosis is a complex chronic side-effect of the stenting treatment. In this study, to reduce stent restenosis and induce re-endothelialization within the artery, we applied coronary stents coated with stem cells secreting angiogenic growth factors via an inducible genome-editing system. After confirming the characteristics of the cells and their adhesion properties on the stents, we transplanted the stents into a swine model to evaluate the restenosis and potential therapeutic use of the stents with stem cells. Restenosis was evaluated via optical coherence tomography (OCT), micro-computed tomography (mCT) and angiography, and re-endothelialization by immunostaining after cardiac stent treatment. Compared to a bare metal stent (BMS) or a parental umbilical cord blood-derived mesenchymal stem cells (UCB-MSC)-coated stent, the stents that had stem cells capable of the controlled release of hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) successfully reduced re-stenosis within the stent and induced natural re-endothelialization. Furthermore, UCB-MSCs exhibited the ability to differentiate into endothelial cells in Matrigel, and HGF and VEGF improved the differentiation. Our study indicates that the stents coated with UCB-MSCs secreting VEGF/HGF reduced the restenosis side effects of cardiac stenting with improved re-endothelialization.

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THERAPEUTIC POTENTIAL OF STEM SELLS AND ZINC ON REDUCTION OF LIVER FIBROSIS

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Globally 1 out of 40 people died due to chronic liver diseases. In case of liver failure, transplantation is the last available therapy but due to lack of donor, graft rejection, operative damage and high cost making this therapy unsuccessful. Stem cells therapies developed new ways to treat liver diseases, but due to oxidative stress at damage site causes poor MSCs proliferation and engraftment. The aim of the current study was to explore the therapeutic potential of $ZnSO_4$ and MSCs on CCl_4 induce hepatic toxicity. In the current study, CCl_4 (1µl/g) was injected intraperitoneally to female BALB/c mice, twice in a week up till 4 weeks to induce liver damage. MSCs was isolated from femoral and tibial bone of Balb/C mice and were cultured for two weeks. These cultured cells and $ZnSO_4$ both were induce separately as well as in combination in mice body. The mice were then classified into 5 groups: negative control, positive control, CCl_4+MSC treated group, CCl_4+$ZnSO_4$ treated group and CCl_4+MSCs+$ZnSO_4$ treated group. The morphological results showed that in contrast to only MSCs therapy, $ZnSO_4$ along with MSCs showed significant therapeutic result on CCl_4 injured mice. Biochemically, serum ALT and total bilirubin level were found to be significantly decreased in mice treated with $ZnSO_4$ and MSCs. Histopathological examination also revealed that both $ZnSO_4$ and MSCs have strong anti-apoptotic effect on CCl_4 injured liver by decreasing the number of apoptotic hepatocytes in both $ZnSO_4$ and MSCs transplanted mice. RT-PCR results at mRNA level also confirm a significant anti-fibrotic effect of $ZnSO_4$ and MSCs (in combination) transplanted mice on fibrotic liver as evidenced show the down-regulation of apoptotic marker (Bax) and enhancing anti-apoptotic (Bcl-xl) and hepatic marker (Albumin). Thus it is concluded that $ZnSO_4$ is a powerful antioxidant and have the ability to enhance the proliferation rate of MSCs.

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EFFECTS OF ADULT MESENCHYMAL STEM CELLS IN THE EPIDERMAL REGENERATION

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Objective: To investigate the effects of the adult mesenchymal stem cells (AMSCs) on the epidermal regeneration, *in vitro* living skin equivalents (LSEs) were reconstructed by co-culture of keratinocytes with each of the different cell types (fibroblasts, adipose-derived stem cells (ADSCs), bone marrow mesenchymal stem cells (BMSCs)) as dermal matrix cells.

Method: Characteristics of the epidermal structures together with keratinocyte growth, differentiation, and basement membrane integrity were analyzed by H&E staining. Additionally, immunohistochemistry was used to study the expression patterns of proteins related with wound healing, epidermal proliferation, differentiation, and basement membrane formation. The author also performed high-throughput mRNA sequencing of three types of dermal matrix cells in order to clarify the causes of differences in characteristics between cultured LSEs. The associated protein expression was evaluated by signal intensity scoring and image analysis using immunofluorescence images.

Results: Compared to fibroblast base LSEs, stem cell based LSEs showed similar appearances to normal skin. It can be assumed that the stem cell based LSE is thicker and more real skin-like due to the increased genes that were grouped as EGF-like domain cluster. Moreover, the basement membrane was clearly identified in the stem cell based LSE. Similar phenomenon was also seen in integrin immunoflourescent staining. We also found that galectin-7 was strongly expressed in stem cell based LSEs which seem to have good ability of keratinocyte differentiation. Activin A was increased in AMSCs in high-throughput mRNA sequencing analysis, and was expressed largely in both epidermal and dermal layers in immunofluorescent staining.

Conclusion: The proteins produced from the stem cells of the LSE affects the basal keratinocytes through paracrine effects, and contribute to epidermal proliferation and keratinocyte migration. Especially, activin A may have an important role in wound healing as a mediator in dermal-epidermal interaction.

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EVALUATION OF HEMATOPOIETIC PROGENITOR CELLS IN PATIENTS WITH TRAUMA HEMORRHAGIC SHOCK AND ITS CORRELATION WITH OUTCOMES

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Background: Hemorrhagic shock accounts up to 50% of early trauma deaths. Hematopoietic failure has been observed in experimental animals and human following shock and injury. One of the facets of bone marrow failure is multiple organ dysfunction syndrome and is commonly seen in patients recovering from severe trauma and hemorrhagic shock. Bone Marrow (BM) dysfunction is associated with mobilization of hematopoietic progenitor cells (HPCs) into peripheral blood. Present study explored the association of peripheral blood HPCs with mortality in trauma hemorrhagic shock patients (T/HS).

Material and Methods: Prospective cohort studies of patients presenting within 8 hrs of injury with T/HS to the Department of Emergency Medicine, Jai Prakash Narayan Apex Trauma Center, All India Institute of Medical Sciences were recruited. Peripheral blood samples were collected in each patient for measurement of peripheral blood HPCs. Peripheral blood progenitor cell (PBPC) quantification was performed by measuring HPCs counts using the hematology analyzer (Sysmex XE-2100). Clinical and laboratory data were prospectively collected after consent. Ethical approval was taken and data was analysed by Stata 11.2.

Results: 39 patients with trauma hemorrhagic shock and 30 normal healthy controls were recruited. HPCs were significantly higher ($P < 0.001$) in the T/HS as compared to control. Among study group, 14 patients died within 24 h. at the hospital admission, and found HPCs concentrations were highly significant (<0.001) in non-survivors (n = 14) when compared with survivors (n = 25) among T/HS patients.

Conclusions: Our studies suggest the peripheral blood HPCs may be early prognostic marker for mortality among patients who presented with trauma hemorrhagic shock on admission.

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INVESTIGATING THE CELLULAR DYNAMICS OF ORGANS DEVELOPMENT AND CANCER USING 3D IMAGING

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In collaboration with her colleague Nai Yang Fu, I implemented a novel 3D-imaging approach (with 3D glasses) to perform innovative multicoloured lineage tracing studies to follow the development and fate of mammary stem cells (MaSC) and descendant progenitor cells *in vivo* in entire mammary gland. As stem cells divide they produce clones of cells; using this imaging technique the fate of these individual clones could be tracked throughout various stages of mammary gland development, including puberty, pregnancy and normal adult homeostasis. This work provided the first *in vivo* evidence for the existence of bipotent MaSCs, which give rise to the two cell lineages that constitute the mammary ducts, the luminal and the myoepithelial cells, as well as the presence of distinct long-lived unipotent progenitor cells. The cellular dynamics observed at different developmental stages support a model in which both stem and progenitor cells drive morphogenesis during puberty, whereas bipotent MaSCs coordinate ductal homeostasis and remodelling of the adult mouse gland (Nature 2014, Nature Comm. 2016, NCB 2017). We have now specialized this 3D technology to detect early aberrant cellular behaviour in models of breast cancer and to visualise how cancerous cells, according to their cell-of-origin, exit normal ductal homeostasis and survive to self-organise into a solid tumour.

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STAGE SPECIFIC DIFFERENTIATION OF WHARTON JELLY DERIVED MESENCHYMAL STEM CELLS TO GENERATE HIGH QUALITY NEURONS

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Neurodegenerative disorders of the central nervous system (CNS) remain as one of the major health concern, accounting for more than 10% of deaths due to different diseases. In neurodegenerative disorders, Alzheimer's disease, Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Multiple system atrophy (MSA) and Huntington disease are the major contributors. The current therapy, which involves medication and deep brain stimulation at advance stage, focuses on symptomatic treatment with none of them being able to counteract the progression of the disease. Keeping in mind the limitations associated with the present treatments, study of cell based therapy has been initiated. In this study we have successfully trans-differentiated Wharton Jelly derived mesenchymal Stem cells (WJ-MSCs) into neuronal fate. WJ-MSCs were chosen for the study because of their hypoimmunogenic, immunomodulatory, and non-tumorigenic property. WJ-MSCs upon treatment with FGF-2 and EGF acquired neuroectodermal fate. Further analysis of these cells confirmed drastic decrease in the expression of MSCs related genes with concomitant expressing of SOX1, the important transcription factor involved in neural fate determination. Moreover, there was a drastic reduction in the number of cells expressing CD73 and CD105, pan-markers of MSCs. These neuroectodermal cells where further induced and differentiated into mature neuronal cells.

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FIBRIN SCAFFOLD COULD PROMOTE SURVIVAL OF THE HUMAN ADIPOSE–DERIVED STEM CELLS DURING DIFFERENTIATION INTO CARDIOMYOCYTE-LIKE CELLS

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Human adipose-derived stem cells (hADSCs) are capable of differentiating into many cells including cardiac cells. Different types of scaffolds are used for cell differentiation, but the best is yet to be determined. In this study, fibrin scaffold (3D) was fabricated using human plasma fibrinogen compared with culture plates (2D) for the growth and differentiation of hADSCs into cardiomyocyte-like cells. For this purpose, after approving the properties of the isolated hADSCs and fibrin scaffold, four biochemical tests were employed to determine the relative growth rate of hADSCs in 2D and 3D cultures. To examine the effects of two different culture systems on cardiomyogenic differentiation, hADSCs were treated with 10 or 50 µM 5-azacytidine (5-Aza) for 24 h and followed until 10 weeks. The results indicated that the growth of hADSCs in 3D significantly increased after the 7th day ($P < 0.05$). Western blot, qRT-PCR and immunochemistry assays were used to evaluate the rate of cardiac differentiation, which showed significantly higher expression of special cardiac genes such as *NKX2.5, Cx43, MLC2v, βMHC, HAND1, HAND2* and *cTnI* ($P < 0.05$) in the treated hADSCs with 50 µM 5-Aza in the 3D group. However, the expression level of the specific cardiac proteins in 3D was not significant using western blot and immunofluorescence staining. In conclusion, this study suggests that the fibrin scaffold with compressive stress of 107.74 kpa can keep the cells alive for 10 weeks and also allows a higher and sooner differentiation of hADSCs into cardiomyocyte-like cells treated with 50 µM 5-Aza.

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IMPLANT OF AUTOLOGOUS ADULTS BONE MARROW STEM CELLS IN HEART FAILURE, FUNCTIONAL CLASS IV

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Objetives: (1) Demonstrate that CD34 + / CD38 (-) Adult Stem Cells in myocardial tissue generate a significant increase in the ejection fraction after implantation. (2) To observe the improvement in the quality of life of the implanted patients, evaluating the reduction of dyspnea and the number of hospitalizations.

Material and methods: A descriptive, observational study of 71 and 88 -year-old patients with a history of CF IV heart failure with severe deteriorated FEY (<30%) who suffered hospitalizations every 15 days, due to biventricular dysfunction. They were submitted to implantation of bone marrow Stem Cells through retrograde venous technique in coronary sinus with balloon occlusion by femoral catheterization. A pre / post implant echocardiogram was indicated for comparisons (7 months) and a post-implant effort ergometry test was performed.

Results: After a period of 210 days, a significant improvement in the ejection fraction of approximately 8% and 14% was observed with respect to the baseline (P:0.05), and a decrease in both hearts mass of 20% (grams). In addition, it was observed that the patients did not have recurrence in hospital admissions successively every 15-20 days, cause congestive heart failure and that there is a remarkable improvement in the quality of life rapidly after the implantation of Stem Cells. The post-implant ergometry test, at 210 days, turned out to be encouraging, since the patient tolerated the stress test greater than 6 minutes.

Conclusion: The implantation of Stem Cells generated a favorable decrease in the number of hospital readmissions of the evaluated patients and showed improvement of their quality of life after no dyspnea CF IV. It was corroborated that there is a significant improvement of the ejection fraction, with decrease of the mass of the implanted organ.

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A NOVEL S100A8/A9 INDUCED FINGERPRINT OF MESENCHYMAL STEM CELLS IS ASSOCIATED WITH ENHANCED WOUND HEALING

Abjihit Basu
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We here investigated a unique capacity of mesenchymal stem cells (MSCs) to re-establish tissue homeostasis using their premonitory potential to sense danger associated molecular pattern (DAMP) and to mount an adaptive response in the interest of tissue repair. Injection of MSCs pretreated with heterodimeric DAMP protein S100A8/A9 into murine full-thickness wounds, led to a significant acceleration of healing even exceeding that of wounds with non-treated MSCs. This correlates with a fundamental reprogramming of the transcriptome in S100A8/A9 treated MSCs as deduced from in-depth validation via global RNAseq, RT-PCR, and immunostaining. We uncovered a network of genes/proteins involved in proteolysis, enhancing macrophage phagocytosis and controlling inflammation, all contributing to profound clean-up of the wound site as well as genes encoding specific extracellular matrix proteins of scar-reduced embryonic tissue repair. This novel MSC transcriptome not only underscores the concept that MSCs are endowed with the unique property of perfectly controlling multiple cells but also holds substantial promise that MSC-based therapies could be extrapolated using refine inductors for fast wound closure.

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