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Anticancer potential of β-Sitosterol in experimental colon cancer

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Asclepias curassavica Linn. is a traditional medicinal plant used by tribal people in the western ghats, India, to treat piles, gonorrhoea, roundworm infestation and abdominal tumours. We have determined the protective effect of β-sitosterol isolated from *A. curassavica* in colon cancer, using *in vitro* and *in vivo* models. The active molecule was isolated, based upon bioassay guided fractionation, and identified as β-sitosterol on spectral evidence. The ability to induce apoptosis was determined by its *in vitro* antiradical activity, cytotoxic studies using human colon adenocarcinoma and normal monkey kidney cell lines, and the expression of β-catenin and proliferating cell nuclear antigen (PCNA) in human colon cancer cell lines (COLO 320 DM). The chemopreventive potential of β-sitosterol in colon carcinogenesis was assessed by injecting 1,2-dimethylhydrazine (DMH, 20mg/kg b.w.) into male Wistar rats and supplementing this with β-sitosterol throughout the experimental period of 16 weeks at 5, 10, and 20 mg/kg b.w. β-sitosterol induced significant dose-dependent growth inhibition of COLO 320 DM cells (IC_{50} 266.2μM), induced apoptosis by scavenging reactive oxygen species, and suppressed the expression of β-catenin and PCNA antigens in human colon cancer cells. β-sitosterol supplementation reduced the number of aberrant crypt and crypt multiplicity in DMH-initiated rats in a dose-dependent manner with no toxic effects. We found doses of 10-20 mg/kg b.w. β-sitosterol to be effective for future *in vivo* studies. β-sitosterol had chemopreventive potential by virtue of its radical quenching ability *in vitro*, with minimal toxicity to normal cells. It also attenuated β-catenin and PCNA expression, making it a potential anticancer drug for colon carcinogenesis.

Alessandra Sacco, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Dystrophin deficiency combined with reduced muscle stem cell reserve in mdx/mTR mice models Duchenne Muscular Dystrophy

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[2]Muscle Development and Regeneration Program, Sanford-Burnham Medical Research Institute, USA
[3]Department of Surgery, Division of Plastic and Reconstructive Surgery, University of California, USA

In Duchenne Muscular Dystrophy (DMD), *dystrophin* mutation leads to progressive lethal skeletal muscle degeneration. Eventually in patients functional muscle tissue is supplanted by fibrosis, calcium deposits and adipose accumulation that coincides with clinical manifestations. Although clearly initiated by dystrophin deficiency, the pathophysiological cause of eventual failure of the tissue repair process is unknown. Unfortunately dystrophin deficiency does not recapitulate DMD in mice (mdx), which have mild skeletal muscle defects and potent regenerative capacity. The absence of a mouse model for DMD that faithfully mimics key features of the human disease has limited our understanding of its pathophysiology and tests of potential therapies. We postulated that human DMD progression is a consequence of loss of muscle stem cell function and that the mild mouse mdx phenotype results from greater reserve fueled by longer telomeres. To test this hypothesis, we crossed dystrophic mdx mice with mice lacking the RNA component of the telomerase enzyme Terc. We report that this novel mouse model has severe muscular dystrophy with profound muscle weakness, elevated serum enzyme levels, and increased muscle fibrosis and calcium deposits. Their muscle stem cells exhibit reduced proliferative and regenerative capacity in vitro and in vivo upon transplantation and their progeny has shortened telomeres. These data suggest that DMD progression results from a cell autonomous failure of muscle stem cells to maintain the damage-repair cycle initiated by dystrophin deficiency. The essential role of muscle stem cell function has implications for treatment approaches for DMD.

Amr Amin, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Saffron: A potential target for a novel anti-cancer drug against hepatocellular carcinoma

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Saffron has been proposed as a promising candidate for cancer chemoprevention. The purpose of this investigation was to investigate the chemopreventive action and the possible mechanisms of saffron against diethylnitrosamine (DEN)-induced liver cancer in rats. Administration of saffron (75 mg/kg per day) started two weeks prior to the DEN injection and was continued for 22 weeks. Saffron significantly reduced the DEN-induced increase in the number and the incidence of hepatic nodules. Saffron also decreased the number and the area of placental glutathione-S-transferase positive foci in livers of DEN-treated rats. Furthermore, saffron counteracted DEN-induced oxidative stress in rats as assessed by restoration of superoxide dismutase, catalase, and glutathione-S-transferase levels and diminishing of myeloperoxidase activity, malondialdehyde and protein carbonyl formation in liver. Immunehistochemistry showed that saffron inhibited the DEN mediated elevations in numbers of cells positive for Ki-67, cyclooxygenase 2, inducible nitric oxide synthase, nuclear factor-kappa Bp-65 and the phosphorylated tumor necrosis factor receptor. Saffron also blocked the depletion in the number of cells positive for TUNEL and M30 CytoDeath in liver tissues of DEN-treated rats. In vitro experiments carried out using HepG2 cells confirmed those findings and showed inhibition of NFkB activation, increased cleavage of caspase-3, and DNA damage and cell cycle arrest upon saffron treatment. The present study provides evidence that saffron exerts a significant chemopreventive effect against liver cancer through inhibition of cell proliferation and induction of apoptosis. This report also shows some evidence that saffron protects rat liver from cancer via modulating oxidative damage and suppressing inflammatory response.

Biography

Prof. Amin is a graduate faculty at UAE University who supervised many graduate theses. He earned his PhD from University of Illinois at Chicago and received a postdoctoral training at University of Pennsylvania School of Medicine. After joining UAEU Prof. Amin's focus was redirected to the field of preventive medicine. His lab is interested in natural product's protection against diabetes and cancer. He has published many articles, reviews and book chapters in reputable journals. He serves on the editorial boards and as a reviewer of many international journals. Prof. Amin is also the recipient of many national and international awards.

Cantinotti M, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Diagnostic, prognostic and therapeutic relevance of assay of b-type natriuretic hormone and related peptides in children with congenital heart diseases

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Background: The aim of this article is to review the diagnostic and prognostic relevance of measurement of Brain Natriuretic Peptide (BNP) and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) in pediatric patients with congenital cardiac diseases (CHD).

Methods: A computerized critical literature search in the National Library of Medicine using the keywords "BNP assay" and "NT-proBNP assay" + neonate/s and newborn/s was performed. We then refined the analysis to include only the studies specifically designed to evaluate the clinical usefulness of BNP and NT-proBNP assays in children with CHD.

Results: Several Authors suggested that BNP/NT-proBNP assay is clinically helpful as a diagnostic and prognostic marker for children with suspected CHD. BNP values are closely age-dependent, even in paediatric age. Unfortunately, accurate reference values of BNP and NT-proBNP assays for neonatal age only recently become available. As a result, the lack of homogenous and accurate decisional levels in the neonatal period greatly limited the clinical impact of BNP assay and also contributed to the production of conflicting results. Regardless of age, there is a great variability in BNP/NT-proBNP values among CHD characterized by different haemodynamic and clinical conditions. In particular, cardiac defects characterized by left ventricular volume and pressure overload usually show a higher BNP response than CHD characterized by right ventricular volume or pressure overload.

Conclusions: BNP and NT-pro BNP may be considered helpful markers in the integrated clinical approach for patients with CHD, especially in the neonatal age. BNP assay cannot replace cardiac imaging (including echocardiography, angiography and magnetic resonance), but provide independent, low cost and complementary information for the evaluation of cardiac function and clinical patient status.

Biography

Massimiliano Cantinotti has Accademic Degree in Medicine and Specialization in Cardiology at University of Pisa, Italy and have Scientipic Society Membership in Pediatric Cardiologist Consultant Fondazione Monasterio, Heart Hospital.

Christian Morsczeck, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Dental stem cells derived from impacted wisdom teeth for regenerative dentistry

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Ectomesenchymal dental stem cells could be feasible tools for dental tissue engineering. Impacted wisdom teeth are an interesting source for dental stem cells. Dental follicle cells (DFCs) are a promising example, since they are capable of differentiation into various dental tissue cells, such as osteoblasts or cement oblasts. Moreover, an additional type of dental stem cells is located in a pad-like tissue adjacent to the apex of the developing tooth, which was designated as the third molar pad. These dental neural crest-derived progenitor cells (dNC-PCs) are considered to have ultipotency of differentiation. This presentation will overview the following areas i) DFCs for studying molecular mechanism of the development of the periodontium, ii) dNC-PCs for studying the development of neural crest-derived bone iii) a comparison of the differentiation of dNC-PCs and DFCs iv) a discussion about the versatility of DFCs and dNC-PCs for regenerative dentistry.

Biography

Christian Oliver Morsczeck, male, studied biology. He received a Diploma in biology from the University of Bochum in 1996 and his PhD from the university cologne in 2000. After short postdoctoral trainings in 2001 he led the dental follicle stem cell project at the Center of advanced European studies and research (Caesar) between January 2002 and february2005. From March 2005untill September 2006 he was employed as a project leader at the Research and Development Department of the Danish Bio Tech Company ACE Biosciences (Odense,DK).In October 2006 he started his recent position as a group leader for stem cell biology at the University of Regensburg. In his career he has published 33 per reviewed papers and is co-inventor of 4 patents. He was reviewer for 13 different journals and is member of 3 editorial boards.

De Schauwer Catharina, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Cultivation of mesenchymal stromal cells from cryopreserved mononuclear cells isolated from equine umbilical cord blood

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[2]Laboratory of Biochemistry, Ghent University, Belgium
[3]Department of Comparative Physiology and Biometrics, Ghent University, Belgium

The therapeutic potential of mesenchymal stromal cells (MSC) for cellular therapy has generated an increasing interest in this type of research. In human, as well as in veterinary medicine, considerable research has been performed on the cryopreservation of expanded MSC, but little information is available on the possibility to cryopreserve the original mononuclear cell fraction. The present study describes a protocol to successfully expand equine MSC after cryopreserving the mononuclear cell fraction of umbilical cord blood (UCB). To this end, the mononuclear cell fraction was isolated from 5 UCB samples using a Percoll gradient and cryopreserved in standard 1.8ml cryotubes at a concentration of 1-2×10^6 cells per ml cold freezing solution. Cells were kept frozen for a minimum of three weeks before thawing. Frozen cryotubes were thawed au bain marie at 37°C. Cell viability after thawing varied around 98%. Approximately 4 × 10^6 cells were seeded in a T25 culture flask in culture medium containing low-glucose DMEM, 30% FCS, 10^{-7} M low dexamethazone, 50 µg/mL gentamycine, 10 µl/ml antibiotic antimycotic solution, 250 ng/mL fungizone and 2 mM ultraglutamine. In 4 out of 5 samples, adherent spindle-shaped cell colonies occurred within 9.8 ± 3.2 days and 80% confluency was reached after 16.3 ± 2.2 days of incubation at 38.5°C and 5% CO_2. After three passages, undifferentiated MSC were immunophenotyped using multi-color flow cytometry. In conclusion, equine MSC can be cultured successfully after cryopreservation of the isolated mononuclear cell fraction, an approach that is time- as well as cost-efficient.

Dina Sabry, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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The clinical use of human culture–expanded autologous bone marrow mesenchymal stem cells transplanted on platelet-rich fibrin glue in the treatment of articular cartilage defects: A pilot study and preliminary results

Dina Sabry

Cairo University, Egypt

Objective: To test the hypothesis that platelet-rich fibrin glue (PR-FG) can be used clinically as a scaffold to deliver autologous culture-expanded bone marrow mesenchymal stem cells (BMMSCs) for cartilage repair and to report clinical results 1 y after implantation of MSCs PR-FG.

Patients and Methods: Autologous BM-MSCs were culture expanded, placed on PR-FG intraoperatively, and then transplanted into 5 full-thickness cartilage defects of femoral condyles of 5 patients and covered with an autologous periosteal flap. Patients were evaluated clinically at 6 and 12 mo by the Lysholm and Revised Hospital for Special Surgery Knee (RHSSK) scores and radiographically by x-rays and magnetic resonance imaging (MRI) at the same time points. Repair tissue in 2 patients was rated arthroscopically after 12 mo using the International Cartilage Repair Society (ICRS) Arthroscopic Score.

Study Design: Case series; level of evidence 4.

Results: All patients' symptoms improved over the follow-up period of 12 mo. Average Lysholm and RHSSK scores for all patients showed statistically significant improvement at 6 and 12 mo postoperatively ($P < 0.05$). There was no statistically significant difference between the 6 and 12 mo postoperative clinical scores ($P = 0.18$). ICRS arthroscopic scores were 8/12 and 11/12 (nearly normal) for the 2 patients who consented to arthroscopy. MRI of 3 patients at 12 mo postoperatively revealed complete defect fill and complete surface congruity with native cartilage, whereas that of 2 patients showed incomplete congruity.

Biography

Dina Sabry has completed his M.D at the age of 33 years from Cairo University. I have published more than 25 papers in reputed journals.

Dmitriy M Chudakov, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Quantitative tracking of individual TCR repertoires

Dmitriy M Chudakov

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The individual repertoire of T Cell Receptors (TCRs) is a mirror of functioning of an immune system that keeps detailed information concerning infectious and autoimmune conditions. We have developed approach that enables unbiased quantitative analysis of the human TCR V beta repertoire by massive sequencing. Using this approach, we have performed the first detailed tracking of the fate of human T cell clones after high dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT). We show that multiple T cell clones do survive the transplantation procedure, some of them being essentially suppressed, but some of them expanding and fighting infections early after HSCT. We believe that wide application of the proposed approach will lead to optimization of HSCT protocols, progress in understanding infection and autoimmunity, and development of individual sequence-based diagnostics of immune status.

Biography

DM Chudakov has completed his PhD at the age of 25 years from Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry, RAS (Moscow, Russia). Starting form 2008, he is a head of the laboratory of Fluorescent instruments for immunology and neurobiology in the same institute. He has published more than 50 papers in reputed journals.

Eric Murillo-Rodriguez, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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A descriptive analysis of the hypocretin cell transplantation diminishing narcoleptic-like sleep disturbances in rats

Eric Murillo-Rodriguez[1], Oscar Arias-Carrion[2], Diana Millan-Aldaco[3], Marcela Palomero-Rivero[3] and Rene Drucker-Colín[3]

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[2]Experimental Neurology, Philipps University, Germany
[3] Neuropatología Molecular, Instituto de Fisiologia Celular, Universidad Nacional Autonoma de Mexico, Mexico

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness, sleep fragmentation, and cataplexy. This disturbance is related with hypocretin (HCRT) system disruption either deficient ligand or dysfunction in HCRT receptors. Studies in experimental narcolepsy models include the genetic KO mice and the dog that lacks the receptor or the ligand. Our group has reported the development of a different experimental model. The injection into lateral hypothalamus (LH) of the neurotoxin named hypocretin-2-saporin (HCRT2/SAP) destroys the HCRT neurons and diminishes the contents of the peptide in the cerebrospinal fluid (CSF) and induces narcoleptic-like behaviour in rats as assessed by EEG/EMG means. Then, if HCRT2/SAP destroys HCRT neurons and leads to narcolepsy, then it is imperative to evaluate whether grafting HCRT neurons into LH of lesioned rats would revert the sleep abnormalities. Here we report that transplantation of HCRT neurons into LH of HCRT2/SAP lesioned rats improved the sleep alterations.

Biography

Eric Murillo-Rodríguez completed his Ph.D at the age of 28 years from Universidad Nacional Autonoma de Mexico (UNAM). Dr. Murillo-Rodríguez was postdoctoral fellow at Harvard University School of Medicine from 2001-2004. He was Associate Researcher at Prof. Rene Drucker-Colín´s lab at UNAM (2005-2007). Dr. Murillo-Rodríguez was holding a Full Professor Appointment at Universidad Autonoma de Campeche (Mexico) from 2007-2009 and currently; he is Full Professor at Universidad Anáhuac Mayab in Merida, Yucatán (Mexico).

Dr. Murillo Rodriguez is part of the review board of journals such as Journal of Neurology, The International Journal of Neuropsychopharmacology, among others. His scientific production includes more than 30 articles published in peer-reviewed scientific journals, 10 chapters in books and numerous participations in domestic and international conferences. Additionally, he is member of several scientific societies, including Society for Neuroscience and Sleep Research Society. Finally, Dr. Murillo Rodríguez has received academic awards, including the Young Investigator Award given by the World Federation of Sleep Research Societies and the Sleep Research Society. He is a member of the National System of Researchers in Mexico (Level 1).

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Ex Vivo observation of human nucleus pulposus chondrocytes isolated from degenerated intervertebral discs

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Southeast University School of Medicine, China

Study Design: We performed an *ex vivo* study to observe cell morphology and viability of human nucleus pulposus (NP) chondrocytes isolated from degenerated intervertebral discs (IVD).

Purpose: To better understand the biological behavior of NP chondrocytes in monolayer cultures.

Overview of Literature: Biological repair of IVDs by cell-based therapy has been shown to be feasible in clinical trials. As one of the most promising transplanting seeds, how the isolated NP chondrocytes behavior *ex vivo* has not been fully understood.

Methods: Human NP chondrocytes were harvested from 20 degenerated IVDs and cultured in monolayers. Histological and immunochemistry staining was used to detect cell morphology change. Cell viability was studied by analyzing cell cycle distribution and apoptotic rate in the primary and subculuted cells.

Results: The round or polygonal primary NP chondrocytes had an average adherence time of 7 days and took nearly 31 days to reach 95% confluence. The spindle-shaped P1 NP chondrocytes increased growth kinetics and took about 12 hours to adhere and 6.6 days to get 95% confluent(Figure1). Immunochemistry staining of collagen II was positive in the cell cytoplasm. Nearly 90% of the confluent NP chondrocytes stayed in G1 phase while 16% underwent apoptosis(Table1). No significant difference of the collagen II expression, cell cycle distribution or the apoptosis indices were detected between the primary and subcultured NP chondrocytes.

Conclusions: Human NP chondrocytes undergo significant morphological change in monolayer cultures. Cell cycle distribution pattern and apoptosis index of the cutured NP chondrocytes potentially influence their clinical transplantation or laboratory use.

Feng Wang has completed his MS degree at the age of 27 years from Southeast University and is doing doctoral studies from Southeast University School of Medicine. He has published 6 papers about the pathogenesis of intervertebral disc degeneration. His laboratory is investigating the phenotype changes of senescent disc cells and how cellular senescence influences the degenerating process of intervertebral disc.

Frank Edenhofer, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Exploring novel pathways of cell reprogramming and transdifferentiation for targeted stem cell therapies

Frank Edenhofer

University of Bonn - Medical Center, Germany

Embryonic stem (ES) cells have become a major focus of scientific interest as a potential source for both, transplantable cells in regenerative medicine, and disease modeling. Human induced pluripotent stem (iPS) cells would represent an appealing option for the use of ES-like patient-specific cells as no embryos or oocytes are required for their derivation. However, crucial safety issues have to be addressed in order to create human iPS cells that are clinically useful as the classical iPS technique involves permanent genetic manipulation that may result in tumor formation. Our research focuses on the derivation of safe iPS cells, targeted differentiation into transplantable neural precursors and its application for disease modeling. In contrast to conventional gene transfer strategies the direct introduction of proteins and synthetic mRNA into cells bypasses the risk of insertional mutagenesis and thus offers an alternative to genetic intervention. We show that protein transduction is a powerful approach to deliver biologically active proteins directly into cells. This paper presents the use of biologically active cell-permeant reprogramming factors to i) induce pluripotency in somatic cells and ii) study the molecular mechanism of reprogramming. Thus far, viral transduction of transcription factors still represents the preferred, most robust reprogramming system. We performed efficient reprogramming transgene removal by cell-permeant recombinases to genetically clean such virally transduced human iPS cells. Finally, novel strategies will be presented for the targeted differentiation into neural lineages employing small molecules and instructive factors.

Biography

Frank Edenhofer, Ph.D., is the Head of the Stem Cell Engineering Group at the Institute of Reconstructive Neurobiology at the University of Bonn, Germany. He gained his PhD in Biochemistry from the Ludwig-Maximilians University of Munich in 1997. During his PhD studies he worked on molecular mechanisms underlying Prion-mediated neurodegeneration under supervision of Ernst-Ludwig Winnacker. In 1998 he joined the laboratory of Klaus Rajewsky (Institute for Genetics, University of Cologne) for a post-doctoral fellowship to train (stem) cell culture and mouse embryo manipulation. After receiving a junior researcher award in 2002 he established a research group at the University of Bonn. He has published more than 35 papers in reputed journals.

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Ape1-mediated Redox signaling in pancreatic cancer stem cell

Gang-Ming Zou

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Pancreatic cancer often has a poor prognosis due to the difficulty to detect and diagnose early. Currently, there are different treatments available for patients with pancreatic cancer, including surgery, radiation therapy and drug therapy, however, for all stages combined, the 1-year relative survival rate is 25%, and the 5-year survival is estimated as less than 5% to 6%. The phenotype of pancreatic cancer stem cells (PCSC) has been identified separately by a research group in University of Michigan in USA and another research group in Germany in 2007; and it has been suggested that PCSC are involved in pancreatic cancer metastasis. The hedgehog pathway is associated with cancer stem cell (CSC) signaling. Combined treatment with gemcitabine and cyclopamine induced tumor regression and decrease in CSC markers and hedgehog signaling. Direct tumor xenografts are a valid platform to test multicompartment therapeutic approaches in pancreatic cancer. We recently reported that Ape1-mediated redox signaling is associated with pancreatic cancer cell growth and migration. Our further study demonstrated that Ape-1 mediated redox signaling is also important is PCSC growth. Consequently, Ape1 redox inhibitor, E3330, might be a candidate in pancreatic cancer therapy through inhibition both pancreatic cancer cell and pancreatic cancer stem cell growth.

Biography

Gang-Ming Zou has completed his Ph.D in 2001 from Paris VI University in France and postdoctoral studies from Johns Hopkins University School of Medicine. He is the professor and principal investigator in Shanghai Cancer Institute, Shanghai Jiaotong University in China. He is the Chief of Section of Stem Cell Biology in the National laboratory of Oncogene and Related Genes in Shanghai Cancer Institute. He has published more than 25 papers in reputed journals, including PNAS, Blood, Oncogene, and Stem Cells etc, His accomplishment include that he identified the relevance between Pu.1 level and early B cell development, and Redox factor Ape1 in stem cell differentiation etc.

Gunter Lepperdinger, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Mesenchymal stem cell ageing: Tissue regeneration, repair and longevity

Gunter Lepperdinger

Austrian Academy of Sciences, Institute for Biomedical Aging Research, Austria

Stem cells play an important role during development and their dysfunction is associated with a variety of diseases. Also the application of stem cells in medical therapeutics is a promising and emerging field. As organ repair and regeneration processes rely on the regulated activity of tissue-borne stem cells, and they may become increasingly compromised with advancing age, major issues in this context are to investigate the changes that occur in MSC with advancing age (1), and more than that whether these changes are causative for age-related deviations such as the accumulation of fat deposits in bone, impaired fracture healing, or de-regulated hematopoiesis. To analytically approach this question, we study primary MSC from bone of differently aged, yet systemically healthy human donors (2). We could demonstrate that MSC numbers barely decline with age. In contrast to that, long-term *in vitro* proliferation potential of explanted MSC was significantly diminished in cells derived from elderly donors. With advancing donor age, MSC raise the expression level of vascular cell adhesion molecule 1, also called CD106, which is also greatly boosted in response to proinflammatory stimuli. Increasing doses of interferon gamma exerted no immediate influence on the proliferative potential of MSC, but distinctly affected their respective commitment to either differentiate towards the adipogenic or osteogenic lineage. Moderately elevated levels of inflammatory stimuli support osteoblastogenesis and are thus instructive for healing processes, while excessive or chronic inflammatory insults promote adipogenic differentiation and adipose upgrowth (3). Besides this phenomenon, we also recognized large interindividual variation between MSC from different donors. Hence, instead of taking chronological donor age as a measure for MSC quality, we next defined age-matched pairs of primary MSC with largely differing proliferation potential in order to stipulate changes related to biological age. Working along this line, many genes were found to be differentially expressed with high statistical significance. Amongst others, one gene that encodes for a secreted product which can act systemically as a hormone with described functions on nerve and immune cells as well as in stress perception was further functionally tested with regard to enhancement of MSC stemness. Exogenous supplementation of the hormone to MSC cultures enhanced self-renewal of MSC and increased their proliferative capacity. Conclusively, MSC that for whatever reasons secrete more of the hormone are capable of maintaining stemness by autocrine cues. More than that, wholesomely fit MSC serve as potent systemic hubs for modulating neuronal and immunological activity.

Jamuna R. Subramaniam, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Induction of neural differentiation, neurite extension and their networking through human umbilical cord derived stromal cells secreted trophic factors

Jamuna R. Subramaniam

Department of Biological Sciences and Bioengineering, Indian Institute of Technology, India

Human umbilical cord is a highly abundant, non controversial source with tremendous potential for Mesenchyma stem cells (MSCs). We derived matrix stromal cells (HUMS) from the human umbilical cord. The HUMS cells secrete several neurotrophic factors. The HUMS cells and their secreted factors are shown to provide some amount of neuroprotection in the neurodegenerative disease models of mice. But the exact mechanism of protection is not well understood. Here, we report that the HUMS cells -secrete six neurotrophic factors, namely, NT-3, NGF, BDNF, VEGF, IGF-1 and GDNF(NFs). These NFs present in the conditioned medium of the HUMS cells induce differentiation, neurite extension and neural networking of a motor neuron cell line, NSC34. These motor neurons express the tyrosine kinase receptors for the above trophic factors (except for BDNF), which are crucial for neurite extension. The tyrosine kinase inhibitor, K252a, drastically reduces CM induced neurite extension. Further, all the 5 TFs need to be neutralized simultaneously with their antibodies to abrogate neurite extension, proving the flexibility and prudent backup mechanism of the system. Intriguingly, none of the phenomenon – differentiation, neurite extension or neural networking required cAMP second messenger system coupling as evidenced by cAMP pathway activator or inhibitor treatment of the NSC34 cells with or without CM.

Biography

Jamuna R. Subtamaniam has completed her Ph.D. from Georgetown University, Washington DC and PDF from Johns Hopkins University, Baltimore. Currently, she is Senior Research Scientist in Indian Institute of Technology Kanpur, India. She has around 17 publications in reputed journals.

Jaspal S. Khillan, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Retinol/vitamin a signaling, stem cells and cancer stem cells

Jaspal S. Khillan
University of Pittsburgh, USA

Natural and synthetic derivatives of retinol, the alcohol form of vitamin A are generally associated with cell differentiation via its metabolite retinoic acid. Contrary to this, we have demonstrated a novel function of retinol in the self-renewal of embryonic stem (ES) cells by activating PI3 kinase signaling pathway via IGFII/IGF1 receptor axis in retinoic acid independent mechanism. Our studies have shown that ES cells do not express the critical retinol metabolizing enzymes and receptor proteins such as STRA6 and CRBP indicating a complete depletion of retinol metabolism in stem cell a property that may be shared by all stem cells including cancer stem cells (CSCs). Retinol supports self renewal of undifferentiated ES and induced pluripotent stem (iPS) cells in the absence of mouse embryonic feeder cells that offers a powerful tool to generate clinically relevant patient specific pluripotent cells for regenerative medicine. An impairment of retinol metabolizing machinery has been reported in many breast cancers. In a significant advancement, a homogenous self renewing population of putative cancer stem cells (CSCs) was created from a mouse mammary tumor. The cells exhibit typical characteristics of stem cells such as unlimited growth, expression alkaline phosphatase and Nanog. These cells are important to investigate the signaling mechanisms of unregulated growth and resistance to therapies and to define genetic profile of CSC to identify novel biomarkers for targeted CSCs without killing the normal breast stem cells for long-term cure of cancer.

Biography

Dr. Khillan is Associate Professor at the University of Pittsburgh at Pennsylvania. His research is focused on the mechanisms of self renewal of stem cells and the mechanisms of tumorigenesis by breast cancer stem cells. He has published more than 50 papers in reputed journals. He is also Director of Transgenic and Gene Targeting Facility.

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Nuclear Ago2 regulates hATSCs survival through direct control of miR10b and SEPN1 expression

Kang Soo Kyung

Seoul National University School of Veterinary Medicine, Republic of Korea

Nuclear Ago2 regulates hATSCs survival through direct control of miR10b and SEPN1 expression; Argonaute 2 (Ago2) has a leading function in miRNA-induced RNA silencing, which is a conserved gene regulatory mechanism in cells and organisms. miRNAs are critical for stem cell self-renewal, development and other functions. We are reporting here that nuclear Ago2 directly controls human adipose tissue-derived stem cell (hATSC) survival in response to a critical dose of reactive oxygen species (ROS)-mediated oxidative cell damage or senescence by binding to a specific region of functional genes. The role of nuclear Ago2 has not been reported. Here, we show that human ATSCs in which Ago2 was downregulated underwent apoptosis. Silencing of Ago2 in hATSCs significantly induces upregulation of miR10b and miR23b expression. These mirs directly interfere with ROS scavenging gene expression, such as TXNL1 and GPX3. Upregulation of miR10b and miR23b is sufficient to induce hATSC cell apoptosis via p38 MAPK phosphorylation and Caspase 3 activation. In addition, Ago2 overexpression or interference of miR10b and miR23b expression in hATSCs partially rescued H_2O_2/ROS-mediated apoptotic cell death by upregulating TXNL2 and JUNK, Caspase 3, and cytochrome C expression. Nuclear Ago2-mediated miR10b and miR23b downregulation also allows cells to escape senescence, which results in TERT activation, stemness overexpression, and improved self-renewal and differentiation through Wnt5a/β-catenin activation. Ago2 expression is critical for stem cells to escape senescence through mir10b and mir23b downregulation. Ago2-binding gene Selenoprotein N1 (SEPN1) was also effectively involved in hATSCs' survival and self-renewal through ROS-mediated p38 MAPK inactivation.

Biography

Prof.Kang has been working in the field of adult stem cell research for 9-10 years. Before appointed as professor at SNU, she was Associate Professor at Pusan National University, Medical school in Korea after postdoctoral training at Tulane gene therapy center and National Primate Research Center in USA. Recently, her main interest in the field of stem cells is somatic cells or adult stem cells reprogramming into more pluripotent stem cells using nontoxic, novel small molecules or proteins. Prof. Kang is a member of the BrainKorea 21 Institute at the College of Veterinary Medicine at SNU, a graduate school to further excellence in training and also engaged in Korea Stem Cell Research Center in Korea as a creative member and main researcher.

Krylova VV, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Some properties of Ca^{2+} pumping ATPase in the symbiosome membrane from broad bean root nodules

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Ca^{2+}-pumping ATPase earlier identified by us in the symbiosome membrane (SM) of broad bean root nodules was functionally characterized by following its catalytic and transport activities. In the experiments with Ca probes arsenazo III and chlorotetracycline, the initial Ca^{2+} pumping rate was shown to achieve optimum at pH 7.2 and to significantly and only slightly decline in the vesicles SM and symbiosomes, respectively, at extreme chosen pH values, 6.0 and 8. 0. It was established that the Ca^{2+}-ATPase is capable of utilizing not only ATP for fueling the Ca^{2+} transport through the SM but also other nucleotide triphosphates but with less efficiency, with its affinity for MgATP ($K_{0.5}$ for MgATP) is ~ 0.1 mM. In the reaction medium without added calcium, the rate of the Ca^{2+}-pumping was found to be markedly stimulated by exogenous calmodulin, a well-known intracellular Ca^{2+}-sensor. Based on the characteristics of Ca^{2+}-dependent ATP/ITP-hydrolysis by symbiosomes using the Ca-EGTA buffer system, an affinity of the Ca^{2+}-ATPase for Ca^{2+} ($K_{0.5}$ for free Ca^{2+}) was shown to be ~ 0.1 μM. In addition, it was found that the rate of Ca^{2+}-dependent ITP hydrolysis by symbiosomes in the presence of KCl in the reaction medium was significantly inhibited by nigericin indicating sensitivity of this process to symbiosome interior alkalinization. This finding and also revealed earlier insensitivity of the Ca^{2+}-ATPase to SM electric polarization are consistent with the proposal that this enzyme uses H^+ as a counterion to facilitate transmembrane calcium translocation. Taken together, these results allow us to refer the SM Ca^{2+}-pump to IIB type Ca^{2+}-ATPases family.

Biography

Krylova V.V. is senior science worker of Timiryazev Institute of Plant Physiology, Russian Academy of Sciences, Moscow. She made her Ph.D. at the problem Ca^{2+} transport across peribacteroid memdrane of broad bean and lupine root nodules. She is author of more than 40 publications, 16 from these in reputed journals.

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Role of liver sinusoidal endothelial cell (LSEC) progenitors in liver regeneration

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[2]Division of Gastrointestinal and Liver Disease, Keck School of Medicine, University of Southern California,USA

Background: Current thinking is that LSEC play an important role in liver regeneration by providing HGF and restoring the microcirculation. However normal LSEC express little HGF. Our hypothesis is that influx of LSEC progenitor cells (PC) provide the increased HGF and are essential for liver regeneration.

Methods: Bone marrow (BM) and peripheral blood CD133+CD45+CD31+ LSEC PC were isolated by magnetic selection. LSEC PC in the liver were isolated from elutriated LSEC. Bone marrow-derived cells were tracked in rats transplanted with BM from GFP+ transgenic rats. Liver regeneration was examined in the two-thirds partial hepatectomy (PHx) model. BM suppression was induced by long bone irradiation. HGF expression was examined by real-time PCR and western blot.

Results: On day 3 following PHx, there was a 1.5-2-fold increase in LSEC PC proliferation (PCNA stain) in BM and in number of LSEC PC in BM and peripheral blood; 25% of LSEC were of BM origin. HGF mRNA and protein in GFP+ LSEC were 4 to 5-fold higher than in GFP- LSEC. On day 5 following PHx, liver weight of BM suppressed rats was 25% lower than controls; LSEC PC or BM infusion on day 1 increased hepatocyte $PCNA^+$ (5.7 ± 1.0 PCNA+ hepatocytes/HPF vs 14.75 ± 1.5 in LSEC PC infused, $p<0.001$) and normalized liver regeneration (liver weight $p<0.0005$: no infusion vs LSEC PC infusion).

Conclusions: Bone marrow LSEC PC are a major contributor to the HGF increase after liver injury. LSEC PC recruitment to the liver is required for normal liver regeneration.

Biography

Assistant professor of Dept. of Hepatic Surgery in Xijing hospital, Xi`an P.R.China. Previously worked in University of Southern California for nearly two years. Mainly worked on liver sinusoidal endothelial cell. Recently found a population of unique progenitor cells for liver sinusoidal endothelial cells. Related findings have been published on Gastroenterology, Hepatology, Plos One etc.

Luca Persano, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Pro-differentiating treatments as effective strategies to target GBM stem-like cells

Luca Persano
University of Padova , Italy

Glioblastoma multiforme (GBM) is the most common malignant brain tumor, currently treated by surgical removal followed by radio- and Temozolomide (TMZ)-based chemotherapy. Although treatment strategies benefit of continuous advances, outcome of GBM patients is still poor. Since the recent definition of GBM cancer stem cells, many researchers are focusing on unravelling the tissue environmental interactions involved in GBM stem cells regulation and maintenance. Aim of our group is the development of novel pro-differentiating treatment able to target the GBM stem-like cell population by itself or sensitize it to chemotherapy in order to induce GBM cell growth inhibition and eventually cell death. In this context we and others recently described the role of BMPs in promoting GBM cell differentiation. Our data show that BMP2, by inhibiting HIF-1α signalling, is able to sensitize GBM stem-like cells to Temozolomide (TMZ)-based chemotherapy and that BMP2/TMZ combined treatment induce strong differentiation and apoptosis of GBM cells resistant to standard therapies.

Unfortunately it has been reported that 20% of GBM displayed epigenetic silencing of BMPR1B due to CpG methylation in its promoter region. Since this patients should not be affected by BMP2 pro-differentiating effects, we analyzed effects mediated by Wnt signalling activation in GBM cells. We found that Wnt pathway activation exerted a strong pro-neuronal differentiation of GBM stem-like cells and that this pro-differentiating effect involved a direct induction of Wnt-regulated pro-neuronal genes and a concomitant Notch signalling inhibition.

In conclusion our data propose two distinct tools to induce strong differentiation of GBM derived stem cells and to effectively target them. Moreover we point to BMP and Wnt signalling activators as promising therapeutic strategies for future GBM management.

Biography

Luca Persano completed his Ph.D in Oncology and Surgical Oncology at the University of Padova in 2008. Since 2004 his research was focused on tumor microenvironment and angiogenesis. He now holds a post-doctoral position on the topic of brain tumor stem cells and their regulation by tumor environmental factors at the University of Padova, Department of Paediatrics headed by Prof. Giuseppe Basso. He has published more than 15 papers in peer-reviewed journals.

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Notch signaling contributes to the maintenance of both normal neural stem cells and patient-derived glioma stem cells

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[2]Department of Medical Genetics and Developmental Biology, State Key Laboratory of Cancer Biology, Fourth Military Medical University, PR China

Background: Cancer stem cells (CSCs) play an important role in the development and recurrence of malignant tumors including glioma. Notch signaling, an evolutionarily conserved pathway mediating direct cell-cell interaction, has been shown to regulate neural stem cells (NSCs) and glioma stem cells (GSCs) in normal neurogenesis and pathological carcinogenesis, respectively. However, how Notch signaling regulates the proliferation and differentiation of GSCs has not been well elucidated.

Methods: We isolated and cultivate human GSCs from glioma patient specimens. Then on parallel comparison with NSCs, we inhibited Notch signaling using g-secretase inhibitors (GSI) and assessed the potential functions of Notch signaling in human GSCs.

Results: Similar to the GSI-treated NSCs, the number of the primary and secondary tumor spheres from GSI-treated GSCs decreased significantly, suggesting that the proliferation and self-renewal ability of GSI-treated GSCs were attenuated. GSI-treated GSCs showed increased differentiation into mature neural cell types in differentiation medium, similar to GSI-treated NSCs. Next, we found that GSI-treated tumor spheres were composed of more intermediate progenitors instead of CSCs, compared with the controls. Interestingly, although inhibition of Notch signaling decreased the ratio of proliferating NSCs in long term culture, we found that the ratio of G2+M phase-GSCs were almost undisturbed on GSI treatment within 72 h.

Conclusions: These data indicate that like NSCs, Notch signaling maintains the patient-derived GSCs by promoting their self-renewal and inhibiting their differentiation, and support that Notch signal inhibitor GSI might be a prosperous candidate of the treatment targeting CSCs for gliomas, however, with GSI-resistance at the early stage of GSCs cell cycle.

Mari Hashitate Dallas, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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29 Nov - 1 Dec 2011 Philadelphia Airport Marriott, USA

Improving immune recovery after Umbilical cord blood transplantation

Mari Hashitate Dallas
St. Jude Children's Research Hospital, USA

Hematopoietic cell transplantation (HSCT) is a potential curative treatment for certain pediatric hematologic and solid malignancies. However, delayed immune reconstitution following HSCT results in prolonged susceptibility to infection and is a major cause of morbidity and mortality. The rate of immune reconstitution is directly correlated with the number of hematopoietic stem cells (HSC) infused and is particularly delayed in patients undergoing umbilical cord blood transplantation (UCBT) secondary to the limited numbers of HSC. Thus, methods to increase the number of umbilical cord blood (UCB) HSC have the potential to accelerate immune reconstitution after UCBT. My previous research involved ex vivo expansion of hematopoietic progenitors with a Notch ligand, Delta1, a known regulator of cell fate determination. We demonstrated that culture of murine hematopoietic progenitors in the presence of Delta1 results in a multi-log increase in the number of precursors that accelerate T cell reconstitution when infused into a mouse model. Furthermore, culture of human UCB progenitors with Delta1 increases the number of progenitors that rapidly engraft in the thymus and accelerate T cell recovery in a mouse model. Data suggest that addition of Delta1-cultured HSC facilitated the thymic engraftment of non-cultured HSC cells. Moreover, significant thymic engraftment of dendritic cells derived from Delta1 cultured cells correlated with rapid immune recovery. Recently, the Dallas lab demonstrated that dendritic cell precursors play a pivotal role in enhancing immune reconstitution after HCT and plays a privitol role in immune recovery after HSCT.

Biography

In 2009, Mari Hashitate Dallas joined the faculty of St. Jude Children's Research Hospital in the Division of Bone Marrow Transplantation to translate her laboratory research to improve the outcome of UCBT. She obtained her degree at the University of California-San Diego in Bioengineering and Neuroscience. Thereafter, she completed her medical training at University of Pennsylvania and her pediatric residency at Children's Hospital of Philadelphia. Dr. Dallas completed her fellowship training at Seattle Children's Hospital while conducting research in stem cell biology at the Fred Hutchinson Cancer Research Center prior to joining the faculty at St. Jude.

Martina Skurlova, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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29 Nov - 1 Dec 2011 Philadelphia Airport Marriott, USA

Immune- modulatory effects of mesenchymal stromal cells in autoimmune joint diseases: May cytokines play a role?

Martina Skurlova

Third Faculty of Medicine, Charles University in Prague, Czech Republic

Bone marrow- derived mesenchymal stromal cells (MSCs) represent a population of non-hematopoietic cells, which can differentiate into various cell types. The cells possess poor immunogenicity and active immunosuppressive capacity profile. Moreover, it was discovered that the immunosuppressive potential of MSCs is not natural, but requires the induction by inflammatory mediators: the cytokines. Interferon- gamma (INF- γ), and contemporary other pro- inflammatory cytokines like tumor- necrosis factor – alpha (TNF- α), interleukin- 1 (IL-1) change functional state of MSCs. Upon inflammation, fluctuations of the INF- γ levels correlate with the loss of alloreactive inducing activity of MSCs. Type of toll-like receptor ligand influences cytokine- profile of MSCs. TLR4- primed MSCs exhibit a pro- inflammatory profile with increased levels of interleukins (IL- 6, and IL- 8), whilst TLR3- primed MSCs develop characteristics of immunosuppressive cells with increased levels of interleukin- 10 (IL- 10).

The rationale for using MSCs in autoimmune joint diseases is their local immunosuppressive and anti-inflammatory activity. *In vitro,* MSC- differentiated chondrocytes from RA patients inhibited collagen type II- stimulated T- cell proliferation and activation by increasing secretion of IL-10 and restoring the secretion of interleukin- 4 (IL-4). *In vivo*, a single injection of MSCs prevented the occurrence of severe damage to bone and cartilage in collagen- induced arthritis model. These data suggest that cytokines may influence the immune-suppressive properties of MSCs in autoimmune joint diseases.

Biography

PharmDr. Martina Skurlova has completed her Ph.D studies at the age of 31 at Third Faculty of Medicine, Charles University in Prague. Now she works as a scientist in the field of rheumatology at the University at the Department of Normal, Pathological, and Clinical Physiology. She participates actively in the pre- and postgraduate education programmes. She has published 10 papers in reputed journals.

Mauricio Rojas, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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29 Nov - 1 Dec 2011 Philadelphia Airport Marriott, USA

Use of mesenchymal stem cells for therapies in the lung

Mauricio Rojas

Division of Pulmonary and Critical Care Medicine, Simmons Center for Interstitial Lung Diseases, McGowan Institute of Regenerative Medicine, University of Pittsburgh, USA

Over the past few years, stem cells has emerged as a possible important therapy on lung disorders. Consistent with this idea, infusion of a specific stem cell populations termed bone marrow derived mesenchymal stem cells (B-MSCs) appear to be important in the regulation of acute inflammatory process. We are presenting examples of the use of B-MSC in acute and chronic diseases in the lung. We demonstrated that B-MSC administration prevented endotoxin induced Acute Lung Injury (ALI), suppressing the endotoxin induced pro-inflammatory cytokines. To demonstrate the clinical relevance of these results, we are presenting new data that will show the association between the ability to induce mobilization of bone marrow derived cells and the survival of patients at the intensive care unit with ALI. Lung transplantation is a viable treatment option for end-stage pulmonary diseases, but development of obliterative bronchiolitis (OB), reduces survival, accounting for 30% of deaths after the third year. In addition, some of the mechanisms used by B-MSC to control injury will be review.

Biography

Being trained as an MD doing basic research, Dr Rojas has a complete perspective to understand the importance of translational medicine. His research on the biology of lung injury and repair, particularly in models of pulmonary fibrosis, acute lung injury and radiation. His research had resulted in the expansion of the understanding of the immune and cellular mechanisms used by mesenchymal stem cells to prevent and control lung injury. Recently, his research focuses on the interactions of mesenchymal stem cells with the micro-environment resulting in important contributions on aging and MSC-extracellular matrix interactions.

Ming hao Zheng, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Autologous tendon progenitor cells therapy for treatment of tendinopathy: From preclinical to clinical trial

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University of Western Australia, Australia

Tendinopathy due to sport injury or over use is one of the most common clinical disorder in musculoskeletal clinics. The chronic degenerative condition frequently does not respond to treatment. In the current study, we propose that autologous tendon progenitor cell therapy (ATT) is effective in preventing tendon degeneration. We have conducted pre-clinical evaluation using a collagenase induced rabbit Achilles tendinopathy model. On the basis of the evaluation and characterisation of tendon cells, we have conducted a phase I trial in patient with refractory lateral epicondylitis.. For pre-clinical study, chronic tendinopathy in rabbit was created in the left Achilles tendon. The result showed that ATT improved tendon remodeling, histological outcomes, collagen content and tensile strength of tendinopathic Achilles tendons. Injected tenocytes were integrated into tendon tissue and could be tracked up to 8 weeks *in vivo*. As the pre-clincial study showed ATT may be a useful treatment of chronic Achilles tendinopathy, we next evaluated the safety and level of efficacy of ATT for treatment of refractory lateral epicondylitis in a pilot study. Cultivated autologous tenocyte from the patellar tendon were injected into the sites of intrasubstance tears and fibrillar discontinuity of the common extensor origin under ultrasound guidance. The interim results demonstrated sixteen patients who reached the 6 month period have shown up to 60% improvement in all scores when compared to pre-treatment. MRI results showed infill of tendon tear in the majority of patients but there was some variation in the quality of regenerated tendon. In conclusions, our study indicates that the feasibility of ATT for the treatment of tendinopathy.

Biography

Professor Ming H Zheng has completed his Bachelor of Medicine from Shantou University in 1983, Ph.D in 1993 and MD in 2000 from the University of Western Australia. He has published more than 120 papers, 8 patents and is serving as an editorial board member of numbers of journals including Stem cell Research and Therapy.He is currently the Director of the Centre for Orthopaedic Research, School of Surgery and Associate Dean of the Faculty of Medicine, Dentistry and Health Sciences at the University of Western Australia. He is also member of Therapeutic Good Committee (human cell and tissue products) at the Therapeutics Goods Administration (TGA) of Australia.

Mrinmay Kumar Mallik, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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29 Nov - 1 Dec 2011 Philadelphia Airport Marriott, USA

A hypothesis and theoretical model speculating the possible role of therapy mediated neoplastic cell loss in promoting the process of glioblastoma relapse

Mrinmay Kumar Mallik

Cytopathology Laboratory Mubarak Hospital Kuwait, Kuwait University, Kuwait

Tumor recurrence is considered to be one of the biggest culprits, behind the poor prognosis of glioblastomas. Using published facts on primary glioblastomas, with special reference to cancer stem cells and their recently described heterogeneity, a hypothesis is being proposed which speculates the possible role of therapy mediated neoplastic cell loss in promoting the process of relapse in these tumors. The mechanisms by which such a phenomenon could be functional, has been integrated into a double version theoretical model, which envisages glioblastomas as neoplasms comprising of multiple, differentially regulated and dynamically distinct neoplastic compartments (named as *active* and *back up* compartments in this article) supported by their own complement of cancer stem cells, wherein therapy mediated cell loss, which mainly affects the size of the active compartment, results in abrogating the inhibitory effect of the active compartment on the back up compartment, thereby leading to the activation of the back up compartment. This activation contributes towards tumor recurrence. The possibility of the existence of such a phenomenon could have strong implications on management and prognosis of these tumors. This work aims to provoke discussion and generate new ideas for further research.

Biography

Dr Mrinmay Kumar Mallik obtained his MD in Pathology from PGIMER Chandigarh India in 1996. Although he works as a clinical cytopathologist at the Cytopathology laboratory his main area of interest since 2005 has been the theoretical aspects regarding cancer stem cells specially cancer stem cells in gliomas. After carefully analyzing a large volume of literature concerning cancer stem cells in gliomas he put forward a novel theoretical model which attempts to explain recurrence in glioblastomas. This was published in the Journal of Theoretical Biology in October 2010.

Raphael Gorodetsky, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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29 Nov - 1 Dec 2011 Philadelphia Airport Marriott, USA

Protein-based biodegradable microspheres can isolate progenitor cells and support their proliferation and differentiation in suspension and serve as cell carriers for tissue regeneration

Raphael Gorodetsky

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In spite of the availability of a wide selection of different types of stem cells and the development of sophisticated biopolymers scaffolds, cells impregnated in implanted 3D structures suffocate and hardly survive and integrate in the damaged tissues following their implantation. We have presented an alternative approach using solid and slowly biodegradable fibrin microbeads (FMB) which were shown to isolate faster mesenchymal stem cell (MSC) from different sources with higher yield than conventional methods. Cells loaded on FMB can expand in-vitro in suspension culture in slow rotation without passages and then be driven to differentiate to the cells needed to repair the target organ. Eventually the slowly degrading non-immunogenic FMB could be serve as cells carriers for their minimally invasive implantation with higher survival rate. This approach has yielded promising results in bone regeneration animal models using MSC from different sources isolated by FMB to repair critical bone defects. This was also proven effective for cartilage differentiation from MSC. Progenitor cells could also be isolated efficiently with FMB from other sources such as fat. We recently showed that matrix dependent cells, including MSC, on FMB can survive for prolonged time intervals of weeks only by being sealed in atmosphere-free vials at room temperature. These findings may have major implications in regenerative medicine based on adult progenitor cells and delivery of cells from the bench to the bed-side. In addition, we propose the mechanism for cell binding to fibrin based matrices, which explains the binding of matrix dependent cells to FMB.

Biography

Professor Raphael Gorodetsky received his BSc, MSc and Ph.D form the Hebrew University, Jerusalem, followed by a postdoc and research position at UCLA Medical Center. In the last 20 years he heads the Laboratory of Biotechnology and Radiobiology at Hadassah Hospital (affiliated to the Hebrew University). Among his research interests is the field of adult stem cells based tissue regeneration. His inventions set the basis for co-founding Hapto Biotech where he served as a chief scientist (later acquired by Forticell). Published 95 papers in reputed journals and recently edited a book on Stem Cells and Tissue Repair (RSC Cambridge, UK).

Savneet Kaur, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Cell therapy and gene therapy using endothelial progenitor cells for neovascularization

Savneet Kaur

School of Biotechnology, Gautam Buddha University, India

Circulating endothelial progenitor cells (EPCs) have been identified for their contribution to revascularization of ischemic tissues. However, despite their promising applications for tissue regeneration, their limited endogenous pool and possible functional impairment associated with a variety of physiological and pathological phenotypes, largely impede their use for autologous transplantation. In the present study, we explored the effect of endothelial nitric oxide synthase (eNOS) gene transfer on the angiogenic potential of *ex vivo* expanded endothelial progenitor cells (EPCs) in a rabbit model of hindlimb ischemia. Rabbit peripheral blood EPCs were cultured and transfected with mammalian expression vector pcDNA3.1-eNOS containing full-length human eNOS gene. Ischemia was induced in the right hind limb of three groups of rabbits by ligation of the distal external iliac artery and excision of the common and superficial femoral arteries. In one group of animals, ten days after the surgery, autologous eNOS-EPCs were transplanted intramuscularly in the ischemic limb. Two other groups received an equivalent number of unmodified EPCs or phosphate buffered saline (PBS) respectively. Two weeks after cell transplantation, the *in vivo* expression of eNOS was detected in limb tissue sections of eNOS-EPCs treated animals. Animals treated with eNOS-EPCs had a significant augmentation in the capillary density and angiographic scores demonstrating distal arterial reconstitution and enhanced angiogenesis in comparison to animals transplanted with EPCs or PBS. The study shows that the modification of EPCs by eNOS constitutes an effective cell and gene therapy to improve the results of vascular regeneration in ischemic diseases.

Biography

Dr Savneet has completed her Ph.D at the age of 27 years from Institute of Genomics and Integrative Biology in the field of innate immunity and postdoctoral studies from Sree Chitra Tirunal Institute for Medical-Sciences and Technology in the area of endothelial progenitor cells and cardiovascular diseases. Presently, she is teaching as an Assistant Professor in the School of Biotechnology in Gautam Buddha University, Greater Noida. She has published about 15 papers in reputed journals and also contributed a chapter in a book published by Indian Academy of Sciences. She is a recipient of several national and international travel awards.

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Hemorrhagic brain metastasis of an amelanotic melanoma foot: A case report

Seema Gupta

Department of Radiotherapy, C.S.M. Medical University, India

Amelanotic melanomas of skin are rare and threatening disease, contributing to less than 5% of all malignant melanomas of skin. Due to lack of any characteristic clinical features, the diagnosis is often based on histopathological and immunohistochemical examinations. The mainstay of treatment is surgical excision followed by adjuvant chemoradiotherapy in advanced stage.

These lesions are frequently diagnosed late in their growth meaning they tend to be deeper and more invasive hence increasing the propensity of distant metastasis making the definitive treatment difficult which leads to poor prognosis. The usual appearance of the metastatic brain lesion in amelanotic melanoma is hypointense on T1-weighted images and hyperintense on T2-weighted images suggestive of lesion with less melanin containing cells, but our patient had an unusual presentation of brain metastasis which was hyperintense on T1-weighted images and hypo to iso intense on T2- weighted images suggestive of hemorrhagic metastasis.

Here we report a 55 years old male who presented initially as a cracked heel with non specific features for a long time period, was diagnosed as an invasive advanced amelanotic melanoma: Clarke's level 5, after 22 months. The lesion was not amenable to complete surgical excision hence limited surgery followed by chemoradiotherapy was done. The patient developed hemorrhagic brain metastasis during the period of treatment for which patient received radiation to brain. Post treatment patient had residual disease in brain and developed new metastatic deposits in popliteal fossa.

Biography

Dr. Seema Gupta works as associate professor in Department of Radiation Oncology, Chhatrapati Shahuji Maharaj Medical University (Upgraded King George's Medical University), Lucknow. Her outstanding & innovative lectures are focused on Head & Neck Cancer. Dr. Gupta is performing two research projects in Molecular Oncology currently; she is recognized in the team for her excellence and the innovation of the work. Beside this; she is guiding a PhD student of doing research work on Oral Cancer specially. Dr. Gupta has research experience of 10 years; She has published more than 25 papers in reputed journal.

Suling Liu, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Micro RNA93 regulates breast cancer stem cells

Suling Liu
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There is increasing evidence that the growth and metastasis of many tumors, including breast cancer, are driven by a cellular population displaying stem cell properties. Like their normal counterparts, these breast cancer stem cells may be regulated by MicroRNAs (miRNAs). We have previously demonstrated that breast cancer cell lines contain subpopulations with stem cell properties that can be isolated by virtue of their expression of Aldehyde dehydrogenase (ALDH) as assessed by the Aldefluor assay. We compared miRNA expression in Aldefluor-positive and Aldefluor-negative populations in a series of five breast cancer cell lines. We identified specific miRNA expression profiles for each population. Among the differentially expressed miRNAs was miR-93 whose expression was significantly increased in Aldefluor-negative compared to Aldefluor-positive populations. To confirm the regulation of miR-93 during cell differentiation we constructed a miR-93 sensor tagged with GFP and demonstrated that sensor-positive (miR-93-negative) cells had significantly increased tumor initiating capacity in NOD/SCID mouse xenografts compared to sensor-negative (miR-93-positive cells). Furthermore, miR-93-negative cells gave rise to tumors containing both miR-93-negative and miR-93-positive cell populations. Utilizing a tetracycline inducible lentivirus driving miR-93 expression, we found that induction of miR-93 expression decreased the ALDH-positive population *in vitro* as well as in mouse xenografts where this reduction was associated with decreased tumor growth. Furthermore, induction of miR-93 expression immediately upon orthotopic implantation or intracardiac injection completely blocked subsequent tumor growth and metastasis formation. These studies demonstrate that miR-93 plays a functional role in the self-renewal and differentiation of breast cancer stem cells. Furthermore, the TET-inducible miR-93 system allows for the controlled regulation of cancer stem cell function providing a valuable model to simulate the effects of CSC-directed therapies on breast cancer growth and metastasis.

Biography

Suling Liu, PhD is an Assistant Professor at the University of Michigan Comprehensive Cancer Center. Her research interests have been focusing on Cancer biology and Stem cell Biology. Evidence from this research is of obvious significance for the development of new diagnosis tools and innovative treatments for cancer. After getting PhD from Ohio State University in Dec 2003, her research interest on breast carcinogenesis took her to focus on cancer therapy to find novel treatments to cancer by targeting the cancer stem cells. This interest brought her to Dr. Max S Wicha's laboratory at the University of Michigan. She has been working on identifying/isolating both normal and cancerous human breast Stem cells and studying the role of Hedgehog pathway, Notch pathway, Bmi-1, BRCA1, tumor microenvironment and microRNAs in the regulation of human mammary stem cell self-renewal and differentiation with most of the molecular and cellular techniques both in vitro and in vivo. She has published over 30 peer-reviewed papers together with three manuscripts in revision and filed four patent applications as a co-inventor; her research has made significant contributions towards out goal of developing more effective therapies for breast cancer.

Swapan Kumar Maiti, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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29 Nov - 1 Dec 2011 Philadelphia Airport Marriott, USA

Animal mesenchymal stem cells: Isolation, proliferation, characterization and orthopedic application

Swapan Kumar Maiti

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The purpose of this study was to isolate, proliferate and application of stem cells (MSC) in bone defects to examine their osteogenic potentiality.

Mesenchymal stem cells were isolated from equine adipose tissues (hrs-AT-MSC) and rabbit bone marrow (r-MSC). The isolated cells were cultured and expanded in optimal cultivation conditions in define culture medium. MSCs were implanted in a bio-ceramic scaffold to repair critical bone defects in 18 New Zealand White adult rabbits (6 each in three groups). hrs-AT-MSC and r-MSC were implanted in groups A & B respectively, whereas, in group C, bone defect kept intact-without MSC. Radiographs were taken at 15 day's interval and histopathological observation was done on day 90 post-implantation.

Primary colonies were observed on day 3 post seeding and first subculture was done on day 7. Cellular morphology of stem cells varied between monolayer of round, elongated spindle-shaped with shorter/longer cytoplasmic extensions and they were grown in single cell or in cluster form. Proliferation capacity of hrs-AT-MSC was much higher than r-MSC. MSCs were characterized by crystal violet, alkaline phosphatase and Integrin alpha.

Radiographs and histopathological findings suggested that the osteogenesis and osseous callus formation to bridge the bone defect was faster and organized in the stem cell construct group of animals. In control group, the bone defect was remained unchanged even at day 90 post implantation.

Mesenchymal stem cells were successfully cultured, proliferate and characterized and finally they were applied in critical bone defect model. MSC possess osteogenic activity and they were immune-privileged.

Biography

Dr Swapan Kumar Maiti has completed his Ph.D from Indian Veterinary Research Institute (Deemed University), Izatnagar (UP) in Veterinary Surgery. He acted as "Visiting Scientist" at University of Leipzig and University of Köln, Germany. He selected two times in International Scientist's Bilateral Exchange Programme. He received prestigious Fellowship from German Research Foundation (DFG), Bonn, Germany (two times) for doing research on animal Stem Cell. Presently, he is engaged on therapeutic application of animal mesenchymal stem cell under a DBT (Directorate of Biotechnology, Govt. of India) project as Principal Investigator. He has published more than 110 research papers in reputed journals.

Valentin Shichkin, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Tumor-specific Anergy vs Global immunosupression in immunity to brain tumors

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Induction of immune response to brain tumors is limited by blood brain barrier that bounds access of naïve T cells to the brain as well as failure of brain environment to activate infiltrating T cells inducing the state of anergy. Anergic T cells are neither deleted nor altered with regard to levels of TCR and co-receptor molecules, but are refractory to the recalling antigenic stimulus. A number of studies also support the hypothesis that tumors evade immunological rejection inducing regulatory $CD4^+CD25^+$ T cells and state of global immunosupression producing TGF-β, IL-10, PG-E2 et al. In this study, mouse B-cell lymphoma engineered to express hemagglutinin (HA) antigen was used as a brain tumor model in which HA-specific $CD4^+$ T cells transferred to syngeneic recipients were monitored during the brain tumor progression. T cells demonstrated the activation already on day 2 after the adoptive transfer and became anergic to day 16. Signs of systemic immunosupression were observed in mice with massive brain tumors and sick symptoms at the late stage of the brain tumor progression. The process is accompanied by very fast reduction of spleen and lymph nodes in symptomatic mice assuming the metabolic stress and corticosteroid emission that dramatically damages the lymphoid organs. However, even at the late stage there still are remaining the tumor-specific T-cells that can be restimulated *in vitro* with HA antigen. Thus, our data suggest at the reasonable conditions the immune response against advanced brain tumors may be reversible at least for some high-resistant $CD4^+$ T cells.

Biography

Prof. Shichkin has got his MS (1981) in Biology from Nizhny Novgorod State University (Russia), PhD (1986) and DSc (1991) in Immunology from Institute of Immunology (Moscow). He then improved his expertise in Immunology in the USA (1998-2003) at the National Cancer Institute – NIH, University of Cincinnati and John Hopkins University. He held academic research positions as a Senior Scientist, Principal Scientist and Laboratory Chief. He is now a professor of Immunology at the University "Ukraine" and Taras Shevchenko National University in Kyiv (Ukraine). He is author more 80 publications in fields of immunobiology, hybridoma technology and cancer immunology.

Valentin Shichkin, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Thymic stem cells as a potential approach for immune system regeneration

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Regenerative potential of pluripotent stromal cells (PSC) of bone marrow, cord blood and adipose tissue is the subject of intensive study, both in terms of experimental studies, and in terms of their clinical application in cell therapy and regenerative medicine. Thymus is a lymphoepithelial organ that also contains the PSC as a structural and functional microenvironment that plays a key role in the development of T cells that control various forms of immune response, protect from infections and are involved in the formation of anti-tumor resistance. The function of thymus gradually weakens with age, is inhibited by stress, physical and cytotoxic effects, including the medical treatment. Thymus partially or completely is removed in some surgical intervention that can cause frequent infections and the risk of tumors as a result of development the secondary immunodeficiency states. Although the ability of thymus to restore after damages is well-known cell sources and mechanisms of the regeneration still studied incompletely. This particularly applies both to the lymphoid and the non-lymphoid thymic components. Our data assumes that the thymus of adult animals and humans contains resident populations of self-renewing cells with the potential of stem cells. These cells may be considered as a source of the thymic regeneration and could be used for autologous transplantation for regenerative restoration of immune system functions at the immunodeficiency resulting from the surgical thymectomy. This idea may be basis for the development of new approaches for compensation of postsurgical immunodeficiency states and improving of the patient life quality.

Biography

Dr. Shichkin has got his MS (1981) in Biology from Nizhny Novgorod State University (Russia), PhD (1986) and DSc (1991) in Immunology from Institute of Immunology (Moscow). He then improved his expertise in Immunology in the USA (1998-2003) at the National Cancer Institute – NIH, University of Cincinnati and John Hopkins University. He held academic research positions as a Senior Scientist, Principal Scientist and Laboratory Chief. He is now a professor of Immunology at the University "Ukraine" and Taras Shevchenko National University in Kyiv (Ukraine). He is author more 80 publications in fields of immunobiology, hybridoma technology and cancer immunology.

Varda R Deutsch, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Clear resolution of different hsc and mk-p bm populations and their subsets in normal and disease states enabled by high definition flow cytometry

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Thrombopoiesis, which is regulated by physiological demand, requires several developmental steps beginning with hematopoietic stem cell (HSC) commitment to Mk progenitors (MK-P) followed by proliferation, terminal Mk maturation and platelet production. While each step in this complex pathway is crucial for platelet production, the Mk-p pool provides the platform for platelet development. Studying Mk-p populations under normal and disease states may provide new insights into the molecular and cellular mechanisms that regulate normal and aberrant thrombopoiesis. The aim of the study was to assess the utility of high definition flow cytometry to provide a high resolution tool for detecting HSC and MK-p and their subpopulations in normal and thrombopoietic disease states. The populations studied were from normal bone marrow-BM, cord blood-CB, mobilized peripheral blood, and BM from Immune Thrombocytopenia Purpura-ITP, chronic myeloid leukemia-CML and essential thrombocythemia-ET. Studying Mk-p populations under different physiological conditions and in disease states has now provided us with new information regarding the populations that contribute to thrombopoiesis. We demonstrate for the first time that the relative proportion of Mk-p and early Mk-p which still maintain CD34 and CD34+ HSPC that have acquired high levels of CD41 are not the same under different physiological conditions. $CD34^+$ and $CD34^+/CD41^+$ cells were increased in PBSC and decreased in CB, correlating with the known shorter platelet nadir in patients transplanted with PBSC and the prolonged thrombocytopenia following CB transplant. In CML and ET, where platelet counts are higher than normal, $CD34^+/CD41^+$ cells were reduced, implying forced maturation of MK-p and facilitated thrombopoiesis. No significant differences were found in the proportion of CD41+ megakaryocyte progenitors ($CD41+/SSC^{low/CD45dim/neg}$) in PBSC and CB compared to normal BM, 0.2%, when analyzed by our recently established method (1). The proportion of Mk-p was 0.2% in ITP, 0.1% in CML with a ten fold increase observed in ET. This population newly defined MK-p population from normal BM and ET was sorted and cloned in full cytokine methocult with the addition of thrombopoietin for CFU-meg and results confirmed these findings. Further analysis of the progenitors in normal BM and PBSC resolved that 1-2% of the MK-p remained early progenitors and maintained CD34. In CB the CD41+ Mk-p population contains no detectable CD34+ cells, once again pointing to lower numbers of transplantable early Mk-p in CB. We further resolved the subpopulations of Mk-p that expressed CD34 in ITP, CML and ET. In ITP and CML a higher proportion of early Mk-p that maintained CD34+ were noted. In ET which is characterized by MK maturation and increase platelet production, the BM contains a relatively larger proportion of Mk-p (which were cloneable), than normal BM (1% vs 0.2%). However, these cells contain only low numbers of CD34+ cells implying accelerated maturation and loss of CD34 on their surface. This notion is supported by the reduced CD34+ CD41+ HSPC mentioned above. Not surprisingly, most normal BM Mk-p are CD33+ (76%). However, this is not the case in PBSC (16%) and CB Mk-p which express lower levels of CD33 (3%). ITP and CML Mk-p also express lower levels of CD33. This study which utilizes the power of high resolution flow cytometry and sorting demonstrates for the first time that the relative proportion of Mk-p and early Mk-p differ under different physiological conditions. Discovering the markers of HSC and Mk-p subsets that vary in normal and disease states may contribute to our understanding of normal and aberrant thrombopoiesis.

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29 Nov - 1 Dec 2011 Philadelphia Airport Marriott, USA

Blockade PDL1 gene expression by siRNA affects the adhesion and migration of human placenta derived mesenchymal stem cells

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It is reported that human placenta derived mesenchymal stem cells(hPMSCs) have strong immunosuppressive properties and exhibit immune-related cell surface markers similar to bone marrow derived mesenchymal stem cells, including being positive for HLA-ABC but negative for HLA-DR and a number of costimulatory molecules, such as PDL1, a negative costimulatory molecule related to T cell activation. Here we investigated whether PDL1 expression on hPMSCs involved in the adhesion and migration of hPMSCs. Culture-expanded hPMSCs showed the typical appearance, immunophenotype, mutiple differentiation capacity, and highly expressed PDL1. RT-PCR and immunofluorescence analysis showed that PDL1 siRNA could be successfully transfected into hPMSCs via liposome transfection method, and the expression of PDL1 could be efficiently blocked. Cell count indicated that the difference of hPMSCs adhesion rate between blockade group and control group was no statistically significant which was observed at half an hour after cell inoculation; but at one hour or three hours after inoculation, the adhesion rate of hPMSCs was significantly higher in the blocked group than that in the control group($P<0.05$). Transwell cell culture system assay showed that hPMSCs migration numbers in blockade group was not significantly different with that in the control group under the culture conditions of SDF1α. However, under the condition of DMEM complete medium or hPMSCs culture supernatant, the migration number of hPMSCs in blockade group significantly reduced ($P<0.05$). Thus we conclude that PDL1 played an important role in the adhesion and migration of hPMSCs, which provides the theoretical basis for the further study of the biological significance of the costimulatory molecules, such as PDL1, expression on hPMSCs.

Biography

Xi-Ying Luan, PhD, is the professor of immunology. She has completed her PhD from Soochow University. She is the director of Immunology, and assistant Dean of School of Basic Medical, Binzhou Medical university. She has published more than 35 papers in reputed journals. She is also a member of the editorial board, Journal of Clinical Rehabilitative Tissue Engineering Research. Dr Luan's research focuses on the molecular mechanisms of costimulatory molecules involved in the regulatory roles of mesenchymal stem cells on immunocytes.

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Reduced intensity and myeloablative conditioning regimens for hematopoietic stem cell transplantation in patients with myeloid and lymphoid malignancies: A meta-analysis

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The reduced intensity conditioning (RIC) stem cell transplantation is widely used for treatment of many hematologic malignancies. This study was undertaken to determine if any significant difference could be found respectively by using RIC versus myeloablative conditioning (MAC) regimen for transplantation on myeloid and lymphoid malignancies and provided the comparison on outcomes in survival and complications.

Methods: We electronically searched the database of Cochrane Central Register of Controlled Trials (CENTRAL), Pubmed, EMbase, and critically appraised all relevant articles (1987.01–2011.03). Comparative studies were carried out on clinical therapeutic effect of RIC and MAC with research on survival, GVHD, relapse, and transplantation related complications (TRM). Meta-analysis was performed by Review Manager 5.0.0.32 software and the funnel plot regression was adopted to assess the publication bias.

Results: We get 1710 records, and 12 studies contained 6 for myeloid malignancies and 6 for lymphoid malignancies totaling 4240 patients have been included. Pooled comparisons of studies of RIC and MAC in transplantation found that different diseases and different conditioning regimen had impact on the outcome. For both myeloid and lymphoid malignancies, compared with MAC regimen, the RIC regimen had significantly lower incidences of TRM (OR=0.56 and 0.52 respectively, P<0.001), higher relapse rates (OR=1.85 and 3.16 respectively, P<0.001) and lower rates of DFS (OR=0.72 and 0.67 respectively, P<0.05), but the overall survival (OS) is similar between the 2 regimens. Patients with myeloid malignancies had significantly lower rates of relapse, higher rates of ≥II degree aGVHD and cGVHD than patients with lymphoid malignancies, and the two types of malignancies have similar rates of DFS.

Conclusions: This meta-analysis confirmed that different regimen has different effect on the outcome and proposed regimen selection for treatment of hematologic malignancies.

Zheng Cui, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.16

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Granulocyte infusion therapy for cancer

Zheng Cui
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Granulocyte infusion therapy for cancer is a new line of cancer treatment based on novel research in cancer-resistant humans and mice and on exceptional therapeutic outcomes of preclinical studies. Over 10 years ago, my lab serendipitously found a unique mouse that was apparently resistant to an array of highly aggressive marine cancer cell lines that would otherwise kill normal mice uniformly. Further studies revealed that this profound cancer-resistance was inheritable in a dominant manner and mediated primarily by the leukocytes of the innate cellular immune system, namely granulocytes and macrophages. The cancer-resistance is naturally-existing without having to be manipulated or stimulated. Upon exposure to cancer cells, effector cells of cancer-resistant mice were rapidly mobilized to migrate to the site of lesion, make tight surface contacts with cancer cells and induce rapid cytolysis of target cells without harming normal tissues or cells. Based on this profound phenotype of cancer-resistance, we developed an *in vitro* assay that can accurately recapitulate the *in vivo* phenotype. This assay measured the normalized ability of effector cells for killing cancer cells and was termed as cancer killing activity or CKA. Using this *in vitro* assay, we were able to find CKA primarily in the granulocyte fraction of white blood cells in some young healthy humans. Based on these observations, we developed a novel therapeutic concept named granulocyte infusion therapy which consists of using CKA assay to identify and to select healthy donors of granulocytes, using apheresis to collect highly purified granulocytes from donors and infusing systemically the freshly collected granulocytes into cancer patients with measurable diseases. Preclinical studies showed that infusion of leukocytes from cancer-resistant donors cured the mice with advanced malignant disease that could not be treated by any other existing cancer therapies. Clinical trials are now underway to evaluate the safety and efficacy of this new therapy in humans.

Biography

Professor Zheng Cui finished his medical degree from China in 1979, his PhD from UMASS at Amherst in 1987 and his postdoctoral training from Harvard Medical School in 1990. He is now a tenured faculty member of Section of Tumor Biology in Department of Pathology, of Department of Cancer Biology, of Institute of Regenerative Medicine, of Programs of Molecular Genetics, of Programs of Molecular Medicine and a member of the Comprehensive Cancer Center of Wake Forest University. He is also an adjunct professor and associate director of Institute of Nanomedicine of Tongji University in Shanghai, China. Professor Cui's work has gained worldwide attention since his first publication on cancer-resistant mice in PNAS in 2003.

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CD44 conjugated liposomes for molecular imaging and herapeutic application in hepatocellular carcinoma

Zongjin Li

Nankai University School of Medicine, China

Conventional therapies target rapidly proliferating non-tumorigenic cells, spare the relatively quiescent cancer stem cells (CSCs) and the CSCs will remain viable after therapy and re-establish the tumor. Thus developing therapeutic strategies to target cancer stem cells to prevent tumor recurrence will be vital for cancer therapy. Here, we developed a new strategy which targets on CSCs by anti-CD44 antibody mediated nanoparticles delivery system loaded with doxorubicin (DOX) or the suicide gene-herpes simplex virus truncated thymidine kinase (TTK), which was fused with renilla luciferase (RL) and RFP (RL-RFP-TTK). The *in situ* liver cancer model was established by injection of 1.0×10^5 HepG2 cells, which carry a reporter system encoding the genes of firefly luciferase and GFP into the liver of NOD/SCID mice. The mice were subsequently treated with ganciclovir (GCV). Then the growth status of tumor was monitored by the optical bioluminescence imaging of firefly luciferase and the specific targeting of the nanoparticles was tracked by imaging of renilla luciferase. Anti-CD44 antibody mediated nanoparticles loaded with Dox or TTK could specifically target the CSCs of HCC, and thereafter were endocytosed by the plasma membrane to transport Dox or the triple fusion (RL-RFP-TTK) into the cells, resulted in the apoptosis of the targeted cells. Taken together, our study demonstrated a novel therapeutic strategy by targeted CSCs of HCC, we also developed a useful multimodality imaging techniques to monitor HepG2 cells' fate *in vivo* and assessed the targeted efficacy of the nanoparticles.

Biography

Zongjin Li has completed his Ph.D from Peking Union Medical College and postdoctoral studies from Stanford University School of Medicine. He is the director of Department of Pathophysiology, and his research focus on molecular imaging and stem cell therapy. He has published more than 27 papers in reputed journals.

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Soluble intracellular adhesion molecule-1 secreted by human umbilical cord blood-derived mesenchymal stem cell reduces amyloid-b plaques

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Presently, co-culture of human umbilical cord blood mesenchymal stem cells (hUCB-MSCs) with BV2 microglia under amyloidβ42(Aβ42) exposure induced a reduction of Aβ42 in the medium as well as an overexpression of the Aβ-degrading enzyme neprilysin (NEP) in microglia. Cytokine array examinations of co-cultured media revealed elevated release of soluble intracellular adhesion molecule-1 (sICAM-1) from hUCB-MSCs. Administration of human recombinant ICAM-1 in BV2 cells and wild-type mice brains induced NEP expression in time- and dose-dependent manners. In co-culturing with BV2 cells under Aβ42 exposure, knockdown of ICAM-1 expression on hUCB-MSCs by small interfering RNA (siRNA) abolished the induction of NEP in BV2 cells as well as reduction of added Aβ42 in the co-cultured media. By contrast, siRNA-mediated inhibition of the sICAM-1 receptor, lymphocyte function-associated antigen-1 (LFA-1), on BV2 cells reduced NEP expression by ICAM-1 exposure. When hUCB-MSCs were transplanted into the hippocampus of a 10-month-old transgenic mouse model of Alzheimer's disease for 10, 20, or 40 days, NEP expression was increased in the mice brains. Moreover, Aβ42 plaques in the hippocampus and other regions were decreased by active migration of hUCB-MSCs toward Aβ deposits. These data suggest that hUCB- MSCs-derived sICAM-1 decreases Aβ plaques by inducing NEP expression in microglia through the sICAM-1/LFA-1 signaling pathway.